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## Mitochondria in chemical-induced toxicity

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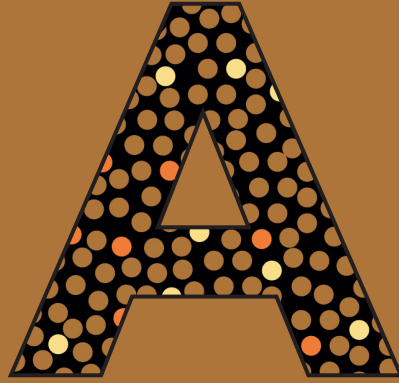
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# Appendix

References

Abbreviations

Nederlandse Samenvatting

List of publications

About the author

## References

- Abozguia, K., Clarke, K., Lee, L., et al. (2006). Modification of myocardial substrate use as a therapy for heart failure. *Nature Clinical Practice Cardiovascular Medicine*, 3(9), 490–498. <https://doi.org/10.1038/npcardio0583>
- Aghamaali, M. R., Jafarian, V., Sariri, R., et al. (2011). Cloning, sequencing, expression and structural investigation of mniopsin from mniopsin leidy: An attempt toward understanding Ca<sup>2+</sup>- regulated photoproteins. *Protein Journal*, 30(8), 566–574. <https://doi.org/10.1007/s10930-011-9363-8>
- Aigner, A., Buesen, R., Gant, T., et al. (2016). Advancing the use of noncoding RNA in regulatory toxicology: Report of an ECETOC workshop. *Regulatory Toxicology and Pharmacology*, 82, 127–139. <https://doi.org/10.1016/j.yrtph.2016.09.018>
- Ainscow, E. K., & Brand, M. D. (1999). Top-down control analysis of ATP turnover, glycolysis and oxidative phosphorylation in rat hepatocytes. *European Journal of Biochemistry*, 263(3), 671–685. <https://doi.org/10.1046/j.1432-1327.1999.00534.x>
- Akimzhanov, A. M., & Boehning, D. (2011). Monitoring dynamic changes in mitochondrial calcium levels during apoptosis using a genetically encoded calcium sensor. *Journal of Visualized Experiments*, 50, 2578. <https://doi.org/10.3791/2579>
- Alaimo, A., Gorojod, R. M., Beauquis, J., et al. (2014). Deregulation of mitochondria-shaping proteins Opa-1 and Drp-1 in manganese-induced apoptosis. *PLoS ONE*, 9(3), e91848. <https://doi.org/10.1371/journal.pone.0091848>
- Alberts, B., Johnson, A., Lewis, J., et al. (2002). *Molecular biology of the cell*. New York: Garland Science.
- Alexander, C., Votruba, M., Pesch, U. E. A., et al. (2000). OPA1, encoding a dynamin-related GTPase, is mutated in autosomal dominant optic atrophy linked to chromosome 3q28. *Nature Genetics*, 26(2), 211–215. <https://doi.org/10.1038/79944>
- Almeida, A., Moncada, S., & Bolaños, J. (2004). Nitric oxide switches on glycolysis through the AMP protein kinase and 6-phosphofructo-2-kinase pathway. *Nature Cell Biology*, 6(1), 45–51. <https://doi.org/10.1038/NCB1080>
- Alvarez, M. J., Shen, Y., Giorgi, F. M., et al. (2016). Functional characterization of somatic mutations in cancer using network-based inference of protein activity. *Nature Genetics*, 48(8), 838–847. <https://doi.org/10.1038/ng.3593>
- Anand, R., Wai, T., Baker, M. J., et al. (2014). The i-AAA protease YME1L and OMA1 cleave OPA1 to balance mitochondrial fusion and fission. *Journal of Cell Biology*, 204(6), 919–929. <https://doi.org/10.1083/jcb.201308006>
- Anderson, N. M., Mucka, P., Kern, J. G., et al. (2018). The emerging role and targetability of the TCA cycle in cancer metabolism. *Protein and Cell*, 9(2), 216–237. <https://doi.org/10.1007/s13238-017-0451-1>
- Anderson, R. E., Tan, W. K., Martin, H. S., et al. (1999). Effects of glucose and PaO<sub>2</sub> modulation on cortical intracellular acidosis, NADH redox state, and infarction in the ischemic penumbra. *Stroke*, 30(1), 160–170. <https://doi.org/10.1161/01.STR.30.1.160>
- Angrish, M. M., McQueen, C. A., Cohen-Hubal, E., et al. (2017). Mechanistic toxicity tests based on an adverse outcome pathway network for hepatic steatosis. *Toxicological Sciences*, 159(1), 159–169. <https://doi.org/10.1093/TOXSCI/KFX121>
- Ankley, G. T., Bennett, R. S., Erickson, R. J., et al. (2010). Adverse outcome pathways: A conceptual framework to support ecotoxicology research and risk assessment. *Environmental Toxicology and Chemistry*, 29(3), 730–741. <https://doi.org/10.1002/etc.34>
- Aschauer, L., Gruber, L. N., Pfaller, W., et al. (2013). Delineation of the Key Aspects in the Regulation of Epithelial Monolayer Formation. *Molecular and Cellular Biology*, 33(13), 2535–2550. <https://doi.org/10.1128/MCB.01435-12>
- Ashburner, M., Ball, C. A., Blake, J. A., et al. (2000). Gene ontology: Tool for the unification of biology. In *Nature Genetics* (Vol. 25, Issue 1, pp. 25–29). <https://doi.org/10.1038/75556>
- Aslam, B., Basit, M., Nisar, M. A., et al. (2017). Proteomics: Technologies and their applications. In *Journal of Chromatographic Science* (Vol. 55, Issue 2, pp. 182–196). <https://doi.org/10.1093/chromsci/bmw167>
- Atienzar, F. A., Blomme, E. A., Chen, M., et al. (2016). Key Challenges and Opportunities Associated with the Use of In Vitro Models to Detect Human DILI: Integrated Risk Assessment and Mitigation Plans. In *BioMed Research International*. Hindawi Limited. <https://doi.org/10.1155/2016/9737920>
- Attene-Ramos, M. S., Huang, R., Michael, S., et al. (2015). Profiling of the Tox21 Chemical Collection for Mitochondrial Function to Identify Compounds that Acutely Decrease Mitochondrial Membrane Potential. *Environmental Health Perspectives*, 123(1), 49–56. <https://doi.org/10.1289/ehp.1408642>
- Auguie, B. (2017). gridExtra: Miscellaneous Functions for “Grid” Graphics. R package version 2.3. <https://CRAN.R-project.org/package=gridExtra>
- Babson, A., & Phillips, G. (1965). A rapid colorimetric assay for serum lactic dehydrogenase. *Clinica Chimica Acta; International Journal of Clinical Chemistry*, 12(2), 210–215. [https://doi.org/10.1016/0009-8981\(65\)90032-X](https://doi.org/10.1016/0009-8981(65)90032-X)
- Baderna, V., Schultz, J., Kearns, L. S., et al. (2020). A novel AFG3L2 mutation close to AAA domain leads to aberrant OMA1 and OPA1 processing in a family with optic atrophy. *Acta Neuropathologica Communications*, 29(8), 93. <https://doi.org/10.1186/s40478-020-00975-w>
- Baird, G. S., Zacharias, D. A., & Tsien, R. Y. (1999). Circular permutation and receptor insertion within green fluorescent proteins. *Proc Natl Acad Sci USA*, 96(20), 11241–11246. <https://doi.org/10.1073/pnas.96.20.11241>
- Bakayan, A., Domingo, B., Vaquero, C. F., et al. (2017). Fluorescent Protein–photoprotein Fusions and Their Applications in Calcium Imaging. In *Photochemistry and Photobiology* (Vol. 93, Issue 2, pp. 448–465). Blackwell Publishing Inc. <https://doi.org/10.1111/php.12682>
- Baker, M. J., Lampe, P. A., Stojanovski, D., et al. (2014). Stress-induced OMA1 activation and autocatalytic turnover regulate OPA1-dependent mitochondrial dynamics. *EMBO Journal*, 33(6), 578–593. <https://doi.org/10.1002/emj.201386474>

- Balaban, R. S., Nemoto, S., & Finkel, T. (2005). Mitochondria, oxidants, and aging. In *Cell* (Vol. 120, Issue 4, pp. 483–495). Cell Press. <https://doi.org/10.1016/j.cell.2005.02.001>
- Balestrino, R., & Schapira, A. H. V. (2020). Parkinson disease. In *European Journal of Neurology* (Vol. 27, Issue 1, pp. 27–42). <https://doi.org/10.1111/ene.14108>
- Ball, A. L., Kamalian, L., Alfirevic, A., et al. (2016). Identification of the additional mitochondrial liabilities of 2-hydroxyflutamide when compared with its parent compound, flutamide in HepG2 cells. *Toxicological Sciences*, 153(2), 341–351. <https://doi.org/10.1093/toxsci/kfw126>
- Ball, N., Cronin, M., Shen, J., et al. (2016). Toward Good Read-Across Practice (GRAP) guidance. *ALTEX*, 33(2), 149–166. <https://doi.org/10.14573/ALTEX.1601251>
- Banaji, M., Mallet, A., Elwell, C. E., et al. (2010). Modelling of mitochondrial oxygen consumption and NIRS detection of cytochrome oxidase redox state. *Advances in Experimental Medicine and Biology*, 662, 285–291. [https://doi.org/10.1007/978-1-4419-1241-1\\_41](https://doi.org/10.1007/978-1-4419-1241-1_41)
- Bannuscher, A., Hellack, B., Bahl, A., et al. (2020). Metabolomics profiling to investigate nanomaterial toxicity in vitro and in vivo. *Nanotoxicology*, 14(6), 807–826. <https://doi.org/10.1080/17435390.2020.1764123>
- Barbour, J. A., & Turner, N. (2014). Mitochondrial stress signaling promotes cellular adaptations. In *International Journal of Cell Biology*. <https://doi.org/10.1155/2014/156020>
- Bartlett, D. W., Clough, J. M., Godfrey, C. R. A., et al. (2001). Understanding the strobilurin fungicides. In *Pesticide Outlook* (Vol. 12, Issue 4, pp. 143–148). <https://doi.org/10.1039/b106300f>
- Bartlett, D., Clough, J., Godwin, J., et al. (2002). The strobilurin fungicides. *Pest Management Science*, 58(7), 649–662. <https://doi.org/10.1002/PS.520>
- Battistoni, M., Di Renzo, F., Menegola, E., et al. (2019). Quantitative AOP based teratogenicity prediction for mixtures of azole fungicides. *Computational Toxicology*, 11, 72–81. <https://doi.org/10.1016/j.comtox.2019.03.004>
- Battogtokh, G., Choi, Y. S., Kang, D. S., et al. (2018). Mitochondria-targeting drug conjugates for cytotoxic, anti-oxidizing and sensing purposes: current strategies and future perspectives. *Acta Pharmaceutica Sinica B*, 8(6), 862–880. <https://doi.org/10.1016/j.apsb.2018.05.006>
- Bavli, D., Prill, S., Ezra, E., et al. (2016). Real-time monitoring of metabolic function in liver-on-chip microdevices tracks the dynamics of Mitochondrial dysfunction. *Proceedings of the National Academy of Sciences of the United States of America*, 113, E2231–E2240. <https://doi.org/10.1073/pnas.1522556113>
- Bazil, J. N., Buzzard, G. T., & Rundell, A. E. (2010). Modeling Mitochondrial Bioenergetics with Integrated Volume Dynamics. *PLoS Computational Biology*, 6(1), e1000632. <https://doi.org/10.1371/journal.pcbi.1000632>
- Beard, D. A. (2005). A biophysical model of the mitochondrial respiratory system and oxidative phosphorylation. *PLoS Computational Biology*, 1(4), 0252–0264. <https://doi.org/10.1371/journal.pcbi.0010036>
- Befroy, D. E., Rothman, D. L., Petersen, K. F., et al. (2012). <sup>31</sup>P-magnetization transfer magnetic resonance spectroscopy measurements of in vivo metabolism. In *Diabetes* (Vol. 61, Issue 11, pp. 2669–2678). *Diabetes*. <https://doi.org/10.2337/db12-0558>
- Ben-Hail, D., Palty, R., & Shoshan-Barmatz, V. (2014). Measurement of mitochondrial Ca<sup>2+</sup> transport mediated by three transport proteins: VDAC1, the NA<sup>+</sup>/CA<sup>2+</sup> exchanger, and the CA<sup>2+</sup> uniporter. *Cold Spring Harbor Protocols*, 2014(2), 161–166. <https://doi.org/10.1101/pdb.top066241>
- Bennekou, S. (2019). Moving towards a holistic approach for human health risk assessment - Is the current approach fit for purpose? *EFSA Journal*. European Food Safety Authority, 17(Suppl 1). <https://doi.org/10.2903/J.EFSA.2019.E170711>
- Benz, R., & McLaughlin, S. (1983). The molecular mechanism of action of the proton ionophore FCCP (carbonyl cyanide p-trifluoromethoxyphenylhydrazone). *Biophysical Journal*, 41(3), 381–398. [https://doi.org/10.1016/S0006-3495\(83\)84449-X](https://doi.org/10.1016/S0006-3495(83)84449-X)
- Berezhkovskiy, L. (2004). Volume of distribution at steady state for a linear pharmacokinetic system with peripheral elimination. *Journal of Pharmaceutical Sciences*, 93(6), 1628–1640. <https://doi.org/10.1002/JPS.20073>
- Berg, J., Hung, Y. P., & Yellen, G. (2009). A genetically encoded fluorescent reporter of ATP:ADP ratio. *Nature Methods*, 6(2), 161–166. <https://doi.org/10.1038/nmeth.1288>
- Berg, S., Kutra, D., Kroeger, T., et al. (2019). ilastik: interactive machine learning for (bio)image analysis. *Nature Methods*, 16(12), 1226–1232. <https://doi.org/10.1038/s41592-019-0582-9>
- Berman, S. B., Pineda, F. J., & Hardwick, J. M. (2008). Mitochondrial fission and fusion dynamics: The long and short of it. In *Cell Death and Differentiation* (Vol. 15, Issue 7, pp. 1147–1152). *Cell Death Differ*. <https://doi.org/10.1038/cdd.2008.57>
- Berthiaume, F., MacDonald, A. D., Kang, Y. H., et al. (2003). Control analysis of mitochondrial metabolism in intact hepatocytes: Effect of interleukin-1 $\beta$  and interleukin-6. *Metabolic Engineering*, 5(2), 108–123. [https://doi.org/10.1016/S1096-7176\(03\)00010-7](https://doi.org/10.1016/S1096-7176(03)00010-7)
- Betarbet, R., Sherer, T. B., MacKenzie, G., et al. (2000). Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nature Neuroscience*, 3(12), 1301–1306. <https://doi.org/10.1038/81834>
- Bhatt, D. P., Chen, X., Geiger, J. D., et al. (2012). A sensitive HPLC-based method to quantify adenine nucleotides in primary astrocyte cell cultures. *Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences*, 889–890, 110–115. <https://doi.org/10.1016/j.jchromb.2012.02.005>
- Binan, L., Mazzaferri, J., Choquet, K., et al. (2016). Live single-cell laser tag. *Nature Communications*, 7(1), 1–8. <https://doi.org/10.1038/ncomms11636>

- Bobko, A. A., Dhimitruka, I., Eubank, T. D., et al. (2009). Trityl-based EPR probe with enhanced sensitivity to oxygen. *Free Radical Biology and Medicine*, 47(5), 654–658. <https://doi.org/10.1016/j.freeradbiomed.2009.06.007>
- Bock, F. J., & Tait, S. W. G. (2020). Mitochondria as multifaceted regulators of cell death. In *Nature Reviews Molecular Cell Biology* (Vol. 21, Issue 2, pp. 85–100). <https://doi.org/10.1038/s41580-019-0173-8>
- Boelsterli, U. A. (2003). *Mechanistic Toxicology: The Molecular Basis of How Chemicals Disrupt Biological Targets*. Taylor & Francis.
- Boelsterli, U. A., & Lim, P. L. K. (2007). Mitochondrial abnormalities—A link to idiosyncratic drug hepatotoxicity? *Toxicology and Applied Pharmacology*, 220(1), 92–107. <https://doi.org/10.1016/j.taap.2006.12.013>
- Boess, F., Kamber, M., Romer, S., et al. (2003). Gene expression in two hepatic cell lines, cultured primary hepatocytes, and liver slices compared to the in vivo liver gene expression in rats: Possible implications for toxicogenomics use of in vitro systems. *Toxicological Sciences*, 73(2), 386–402. <https://doi.org/10.1093/toxsci/kfg064>
- Bois, F. Y., Ochoa, J. G. D., Gajewska, M., et al. (2017). Multiscale modelling approaches for assessing cosmetic ingredients safety. *Toxicology*, 392, 130–139. <https://doi.org/10.1016/j.tox.2016.05.026>
- Bokkers, B. G. H., Mengelers, M. J., Bakker, M. I., et al. (2017). APROBA-Plus: A probabilistic tool to evaluate and express uncertainty in hazard characterization and exposure assessment of substances. *Food and Chemical Toxicology*, 110, 408–417. <https://doi.org/10.1016/j.fct.2017.10.038>
- Bollard, M. E., Contel, N. R., Ebbels, T. M. D., et al. (2010). NMR-based metabolic profiling identifies biomarkers of liver regeneration following partial hepatectomy in the rat. *Journal of Proteome Research*, 9(1), 59–69. <https://doi.org/10.1021/pr900200v>
- Bondi, H., Zilocchi, M., Mare, M. G., et al. (2016). Dopamine induces mitochondrial depolarization without activating PINK1-mediated mitophagy. *Journal of Neurochemistry*, 136(6), 1219–1231. <https://doi.org/10.1111/jnc.13506>
- Bonora, M., Giorgi, C., Bononi, A., et al. (2013). Subcellular calcium measurements in mammalian cells using jellyfish photoprotein aequorin-based probes. *Nature Protocols*, 8(11), 2105–2118. <https://doi.org/10.1038/nprot.2013.127>
- Boon, R., Kumar, M., Tricot, T., et al. (2020). Amino acid levels determine metabolism and CYP450 function of hepatocytes and hepatoma cell lines. *Nature Communications*, 11(1). <https://doi.org/10.1038/s41467-020-15058-6>
- Bouhifd, M., Hartung, T., Hogberg, H. T., et al. (2013). Review: Toxicometabolomics. In *Journal of Applied Toxicology* (Vol. 33, Issue 12, pp. 1365–1383). <https://doi.org/10.1002/jat.2874>
- Bouillot, S., Reboud, E., & Huber, P. (2018). Functional consequences of calcium influx promoted by bacterial pore-forming toxins. In *Toxins* (Vol. 10, Issue 10, p. 387). <https://doi.org/10.3390/toxins10100387>
- Bricker, D. K., Taylor, E. B., Schell, J. C., et al. (2012). A mitochondrial pyruvate carrier required for pyruvate uptake in yeast, *Drosophila*, and humans. *Science*, 337(6090), 96–100. <https://doi.org/10.1126/science.1218099>
- Brockmeier, E. K., Hodges, G., Hutchinson, T. H., et al. (2017). The role of omics in the application of adverse outcome pathways for chemical risk assessment. *Toxicological Sciences*, 158(2), 252–262. <https://doi.org/10.1093/toxsci/kfx097>
- Brodie, E. J., Zhan, H., Saiyed, T., et al. (2018). Perrault syndrome type 3 caused by diverse molecular defects in CLPP. *Scientific Reports*, 8(1), 12862. <https://doi.org/10.1038/s41598-018-30311-1>
- Brodland, G. W. (2015). How computational models can help unlock biological systems. In *Seminars in Cell and Developmental Biology* (Vols. 47–48, pp. 62–73). Academic Press. <https://doi.org/10.1016/j.semcdb.2015.07.001>
- Bross, P., & Fernandez-Guerra, P. (2016). Disease-associated mutations in the HSPD1 gene encoding the large subunit of the mitochondrial HSP60/HSP10 chaperonin complex. In *Frontiers in Molecular Biosciences* (Vol. 3, p. 49). <https://doi.org/10.3389/fmolb.2016.00049>
- Brunmair, B., Staniek, K., Gras, F., et al. (2004). Thiazolidinediones, Like Metformin, Inhibit Respiratory Complex I: A Common Mechanism Contributing to Their Antidiabetic Actions? *Diabetes*, 53(4), 1052–1059. <https://doi.org/10.2337/diabetes.53.4.1052>
- Buesen, R., Chorley, B. N., da Silva Lima, B., et al. (2017). Applying ‘omics technologies in chemicals risk assessment: Report of an ECETOC workshop. *Regulatory Toxicology and Pharmacology*, 91 Suppl(Suppl 1), S3–S13. <https://doi.org/10.1016/j.yrtph.2017.09.002>
- Bulthuis, E. P., Adjobo-Hermans, M. J. W., Willems, P. H. G. M., et al. (2019). Mitochondrial Morphofunction in Mammalian Cells. In *Antioxidants and Redox Signaling* (Vol. 30, Issue 18, pp. 2066–2109). <https://doi.org/10.1089/ars.2018.7534>
- Bushel, P. R., Paules, R. S., & Auerbach, S. S. (2018). A Comparison of the TempO-Seq S1500+ Platform to RNA-Seq and Microarray Using Rat Liver Mode of Action Samples. *Frontiers in Genetics*, 9(485). <https://doi.org/10.3389/fgen.2018.00485>
- Busquet, F., A, K., C, R., et al. (2020). New European Union statistics on laboratory animal use - what really counts! *ALTEX*, 37(2), 167–186. <https://doi.org/10.14573/ALTEX.2003241>
- Buzkova, J., Nikkanen, J., Ahola, S., et al. (2018). Metabolomes of mitochondrial diseases and inclusion body myositis patients: treatment targets and biomarkers. *EMBO Molecular Medicine*, 10(12), e9091. <https://doi.org/10.15252/emmm.201809091>
- Caboni, P., Sherer, T., Zhang, N., et al. (2004). Rotenone, deguelin, their metabolites, and the rat model of Parkinson’s disease. *Chemical Research in Toxicology*, 17(11), 1540–1548. <https://doi.org/10.1021/TX049867R>
- Callegaro, G., Kunnen, S. J., Trairatphisan, P., et al. (2021). The human hepatocyte TXG-MAPr: WGCNA transcriptomic modules to support mechanism-based risk assessment. *BioRxiv*, 2021.05.17.444463. <https://doi.org/10.1101/2021.05.17.444463>
- Cannon, J., Tapias, V., Na, H., et al. (2009). A highly reproducible rotenone model of Parkinson’s disease. *Neurobiology of Disease*, 34(2), 279–290. <https://doi.org/10.1016/J.NBD.2009.01.016>
- Carbon, S., Douglass, E., Good, B. M., et al. (2021). The Gene Ontology resource: enriching a GOLD mine. *Nucleic Acids Research*, 49(D1), D325–D334. <https://doi.org/10.1093/nar/gkaa1113>

- Carlson, M. (2019). org.Hs.eg.db: Genome wide annotation for Human. R package version 3.8.2. <https://bioconductor.org/packages/release/data/annotation/html/org.Hs.eg.db.html>
- Carr, D. ported by Nicholas Lewin-Koh, Martin Maechler and contains copies of lattice functions written by Deepayan Sarkar (2021). hexbin: Hexagonal Binning Routines. R package version 1.28.2. <https://CRAN.R-project.org/package=hexbin>
- Cassarino, D. S., Swerdlow, R. H., Parks, J. K., et al. (1998). Cyclosporin A increases resting mitochondrial membrane potential in SY5Y cells and reverses the depressed mitochondrial membrane potential of Alzheimer's disease cybrids. *Biochemical and Biophysical Research Communications*, 248(1), 168–173. <https://doi.org/10.1006/bbrc.1998.8866>
- Celardo, I., Lehmann, S., Costa, A. C., et al. (2017). dATF4 regulation of mitochondrial folate-mediated one-carbon metabolism is neuroprotective. *Cell Death & Differentiation* 2017 24:4, 24(4), 638–648. <https://doi.org/10.1038/cdd.2016.158>
- Chan, E. Y. L., & McQuibban, G. A. (2013). The mitochondrial rhomboid protease: Its rise from obscurity to the pinnacle of disease-relevant genes. In *Biochimica et Biophysica Acta - Biomembranes* (Vol. 1828, Issue 12, pp. 2916–2925). <https://doi.org/10.1016/j.bbamem.2013.05.012>
- Chandel, N. S. (2014). Mitochondria as signaling organelles. In *BMC Biology* (Vol. 22, Issue 2, pp. 204–206). <https://doi.org/10.1186/1741-7007-12-34>
- Chang, T., Horal, M., Jain, S., et al. (2003). Oxidant regulation of gene expression and neural tube development: Insights gained from diabetic pregnancy on molecular causes of neural tube defects. *Diabetologia*, 46(4), 538–545. <https://doi.org/10.1007/S00125-003-1063-2>
- Chang, W., Wickham, H. (2020). ggvis: Interactive Grammar of Graphics. R package version 0.4.7. <https://CRAN.R-project.org/package=ggvis>
- Chang, W., Cheng, J., Allaire, J. J., Sievert, C., Schloerke, B., Xie, Y., Allen, J., McPherson, J., Dipert, A., Borges, B. (2021). shiny: Web Application Framework for R. R package version 1.6.0. <https://CRAN.R-project.org/package=shiny>
- Chen, C., Stephenson, M. C., Peters, A., et al. (2018). 31P magnetization transfer magnetic resonance spectroscopy: Assessing the activation induced change in cerebral ATP metabolic rates at 3 T. *Magnetic Resonance in Medicine*, 79(1), 22–30. <https://doi.org/10.1002/mrm.26663>
- Chen, H., & Chan, D. C. (2009). Mitochondrial dynamics-fusion, fission, movement, and mitophagy-in neurodegenerative diseases. *Human Molecular Genetics*, 18(R2), R169–R176. <https://doi.org/10.1093/hmg/ddp326>
- Chen, L., Zhong, F., & Zhu, J. (2020). Bridging targeted and untargeted mass spectrometry-based metabolomics via hybrid approaches. In *Metabolites* (Vol. 10, Issue 9, p. 348). <https://doi.org/10.3390/metabo10090348>
- Christen, T., Bouzat, P., Pannetier, N., et al. (2014). Tissue oxygen saturation mapping with magnetic resonance imaging. *Journal of Cerebral Blood Flow and Metabolism*, 34(9), 1550–1557. <https://doi.org/10.1038/jcbfm.2014.116>
- Civiletto, G., Varanita, T., Cerutti, R., et al. (2015). Opa1 overexpression ameliorates the phenotype of two mitochondrial disease mouse models. *Cell Metabolism*, 21(6), 845–854. <https://doi.org/10.1016/j.cmet.2015.04.016>
- Clark, L. C., Wolf, R., Granger, D., et al. (1953). Continuous recording of blood oxygen tensions by polarography. *Journal of Applied Physiology*, 6(3), 189–193. <https://doi.org/10.1152/jappl.1953.6.3.189>
- Conboy, E., Selcen, D., Brodsky, M., et al. (2018). Novel Homozygous Variant in TTC19 Causing Mitochondrial Complex III Deficiency with Recurrent Stroke-Like Episodes: Expanding the Phenotype. *Seminars in Pediatric Neurology*, 26, 16–20. <https://doi.org/10.1016/J.SPEN.2018.04.003>
- Consolato, F., Maltecca, F., Tulli, S., et al. (2018). m-AAA and i-AAA complexes coordinate to regulate OMA1, the stress-activated supervisor of mitochondrial dynamics. *Journal of Cell Science*, 131(7), jcs.213546. <https://doi.org/10.1242/jcs.213546>
- Contag, C. H., Spilman, S. D., Contag, P. R., et al. (1997). Visualizing Gene Expression in Living Mammals Using a Bioluminescent Reporter. *Photochemistry and Photobiology*, 66(4), 523–531. <https://doi.org/10.1111/j.1751-1097.1997.tb03184.x>
- Cortassa, S., Aon, M. A., Marbán, E., et al. (2003). An integrated model of cardiac mitochondrial energy metabolism and calcium dynamics. *Biophysical Journal*, 84(4), 2734–2755. [https://doi.org/10.1016/S0006-3495\(03\)75079-6](https://doi.org/10.1016/S0006-3495(03)75079-6)
- Costa-Mattioli, M., & Walter, P. (2020). The integrated stress response: From mechanism to disease. *Science (New York, N.Y.)*, 368(6489). <https://doi.org/10.1126/SCIENCE.AAT5314>
- Craig, A., Sidaway, J., Holmes, E., et al. (2006). Systems toxicology: Integrated genomic, proteomic and metabolomic analysis of methapyriline induced hepatotoxicity in the rat. *Journal of Proteome Research*, 5(7), 1586–1601. <https://doi.org/10.1021/pr0503376>
- Cribbs, J. T., & Strack, S. (2007). Reversible phosphorylation of Drp1 by cyclic AMP-dependent protein kinase and calcineurin regulates mitochondrial fission and cell death. *EMBO Reports*, 8(10), 939–944. <https://doi.org/10.1038/sj.embor.7401062>
- Crouch, S. P. M., Kozłowski, R., Slater, K. J., et al. (1993). The use of ATP bioluminescence as a measure of cell proliferation and cytotoxicity. *Journal of Immunological Methods*, 160(1), 81–88. [https://doi.org/10.1016/0022-1759\(93\)90011-U](https://doi.org/10.1016/0022-1759(93)90011-U)
- Cui, Y., & Paules, R. S. (2010). Use of transcriptomics in understanding mechanisms of drug-induced toxicity. *Pharmacogenomics*, 11(4), 573–585. <https://doi.org/10.2217/pgs.10.37>
- Da Cunha, F. M., Torelli, N. Q., & Kowaltowski, A. J. (2015). Mitochondrial Retrograde Signaling: Triggers, Pathways, and Outcomes. In *Oxidative Medicine and Cellular Longevity* (Vol. 2015, p. 482582). <https://doi.org/10.1155/2015/482582>
- Danhier, P., & Gallez, B. (2015). Electron paramagnetic resonance: A powerful tool to support magnetic resonance imaging research. *Contrast Media and Molecular Imaging*, 10(4), 266–281. <https://doi.org/10.1002/cmmi.1630>
- Daun, S., Rubin, J., Vodovotz, Y., et al. (2008). Equation-based models of dynamic biological systems. *Journal of Critical Care*, 23(4), 585–594. <https://doi.org/10.1016/j.jcrc.2008.02.003>

- Davis, J. M., Ekman, D. R., Skelton, D. M., et al. (2017). Metabolomics for informing adverse outcome pathways: Androgen receptor activation and the pharmaceutical spironolactone. *Aquatic Toxicology*, 184, 103–115. <https://doi.org/10.1016/j.aquatox.2017.01.001>
- De Castro, I. P., Martins, L. M., & Tufi, R. (2010). Mitochondrial quality control and neurological disease: An emerging connection. *Expert Reviews in Molecular Medicine*, 12, e12. <https://doi.org/10.1017/S1462399410001456>
- De Vos, K. J., & Sheetz, M. P. (2007). Visualization and Quantification of Mitochondrial Dynamics in Living Animal Cells. *Methods in Cell Biology*, 80, 627–682. [https://doi.org/10.1016/S0091-679X\(06\)80030-0](https://doi.org/10.1016/S0091-679X(06)80030-0)
- DeBerardinis, R. J., & Chandel, N. S. (2020). We need to talk about the Warburg effect. In *Nature Metabolism* (Vol. 2, Issue 2, pp. 127–129). Nature Research. <https://doi.org/10.1038/s42255-020-0172-2>
- Degli Esposti, M. (1998). Inhibitors of NADH-ubiquinone reductase: an overview. *Biochimica et Biophysica Acta*, 1364(2), 222–235. [https://doi.org/10.1016/S0005-2728\(98\)00029-2](https://doi.org/10.1016/S0005-2728(98)00029-2)
- Degli Esposti, M., & Ghelli, A. (1994). The mechanism of proton and electron transport in mitochondrial complex I. *Biochimica et Biophysica Acta*, 1187(2), 116–120. [https://doi.org/10.1016/0005-2728\(94\)90095-7](https://doi.org/10.1016/0005-2728(94)90095-7)
- Delettre, C., Lenaers, G., Griffoin, J. M., et al. (2000). Nuclear gene OPA1, encoding a mitochondrial dynamin-related protein, is mutated in dominant optic atrophy. *Nature Genetics*, 26(2), 207–210. <https://doi.org/10.1038/103879936>
- Delp, J., Cediel-Ulloa, A., Suci, I., et al. (2021). Neurotoxicity and underlying cellular changes of 21 mitochondrial respiratory chain inhibitors. *Archives of Toxicology*, 95(2), 591–651. <https://doi.org/10.1007/s00204-020-02970-5>
- Delp, J., Funke, M., Rudolf, F., et al. (2019). Development of a neurotoxicity assay that is tuned to detect mitochondrial toxicants. *Archives of Toxicology*, 93(6), 1585–1608. <https://doi.org/10.1007/s00204-019-02473-y>
- Dempsey, J. L., & Cui, J. Y. (2017). Long non-coding RNAs: A novel paradigm for toxicology. In *Toxicological Sciences* (Vol. 155, Issue 1, pp. 3–21). <https://doi.org/10.1093/toxsci/kfw203>
- Dent, M., Amaral, R. T., Da Silva, P. A., et al. (2018). Principles underpinning the use of new methodologies in the risk assessment of cosmetic ingredients. *Computational Toxicology*, 7, 20–26. <https://doi.org/10.1016/J.COMTOX.2018.06.001>
- Depaoli, M. R., Bischof, H., Eroglu, E., et al. (2019). Live cell imaging of signaling and metabolic activities. In *Pharmacology and Therapeutics* (Vol. 202, pp. 98–119). Elsevier Inc. <https://doi.org/10.1016/j.pharmthera.2019.06.003>
- Detaille, D., Guigas, B., Leverve, X., et al. (2002). Obligatory role of membrane events in the regulatory effect of metformin on the respiratory chain function. *Biochemical Pharmacology*, 63(7), 1259–1272. [https://doi.org/10.1016/S0006-2952\(02\)00858-4](https://doi.org/10.1016/S0006-2952(02)00858-4)
- Dey, K., Bazala, M. A., & Kuznicki, J. (2020). Targeting mitochondrial calcium pathways as a potential treatment against Parkinson's disease. *Cell Calcium*, 89, 102216. <https://doi.org/10.1016/j.ceca.2020.102216>
- Dhillon, A. S., Tarbutton, G. L., Levin, J. L., et al. (2008). Pesticide/environmental exposures and Parkinson's disease in East Texas. *Journal of Agromedicine*, 13(1), 37–48. <https://doi.org/10.1080/10599240801986215>
- Di Virgilio, F., Pinton, P., & Falzoni, S. (2016). Assessing extracellular ATP as danger signal in vivo: The pmeluc system. In *Methods in Molecular Biology* (Vol. 1417, pp. 115–129). Humana Press Inc. [https://doi.org/10.1007/978-1-4939-3566-6\\_7](https://doi.org/10.1007/978-1-4939-3566-6_7)
- Di, Z., Herpers, B., Fredriksson, L., et al. (2012). Automated Analysis of NF-κB Nuclear Translocation Kinetics in High-Throughput Screening. *PLoS ONE*, 7(12), e52337. <https://doi.org/10.1371/journal.pone.0052337>
- Diepart, C., Verrax, J., Calderon, P. B., et al. (2010). Comparison of methods for measuring oxygen consumption in tumor cells in vitro. *Analytical Biochemistry*, 396(2), 250–256. <https://doi.org/10.1016/j.ab.2009.09.029>
- Dikoglu, E., Alfaiz, A., Gorna, M., et al. (2015). Mutations in LONP1, a mitochondrial matrix protease, cause CODAS syndrome. *American Journal of Medical Genetics, Part A*, 167(7), 1501–1509. <https://doi.org/10.1002/ajmg.a.37029>
- diMauro, S., & Vivo, D. C. De. (1999). Diseases of Mitochondrial Metabolism. In *Basic: Neurochemistry: Molecular, Cellular and Medical Aspects* (Vol. 6). Lippincott-Raven. <https://www.ncbi.nlm.nih.gov/books/NBK27914/>
- Divakaruni, A. S., Paradise, A., Ferrick, D. A., et al. (2014). Analysis and interpretation of microplate-based oxygen consumption and pH data. In *Methods in Enzymology* (Vol. 547, Issue C, pp. 309–354). Academic Press Inc. <https://doi.org/10.1016/B978-0-12-801415-8.00016-3>
- Dmitriev, R. I., & Papkovsky, D. B. (2012). Optical probes and techniques for O<sub>2</sub> measurement in live cells and tissue. In *Cellular and Molecular Life Sciences* (Vol. 69, Issue 12, pp. 2025–2039). Cell Mol Life Sci. <https://doi.org/10.1007/s00018-011-0914-0>
- Dolman, N. J., Chambers, K. M., Mandavilli, B., et al. (2013). Tools and techniques to measure mitophagy using fluorescence microscopy. In *Autophagy* (Vol. 9, Issue 11, pp. 1653–1662). Taylor and Francis Inc. <https://doi.org/10.4161/auto.24001>
- Doull's, & Casarett. (2008). *Toxicology The Basic Science of Poisons*. In McGraw-Hill. <https://doi.org/10.1036/0071470514>
- Dowle, M., Srinivasan, A., (2021). data.table: Extension of 'data.frame'. R package version 1.14.0. <https://CRAN.R-project.org/package=data.table>
- Dreier, D. A., Mello, D. F., Meyer, J. N., et al. (2019). Linking Mitochondrial Dysfunction to Organismal and Population Health in the Context of Environmental Pollutants: Progress and Considerations for Mitochondrial Adverse Outcome Pathways. *Environmental Toxicology and Chemistry*, 38(8), 1625–1634. <https://doi.org/10.1002/etc.4453>
- Durand, F., & Hoogenraad, N. (2017). Assessing mitochondrial unfolded protein response in mammalian cells. In *Methods in Molecular Biology* (Vol. 1567, pp. 363–378). Humana Press Inc. [https://doi.org/10.1007/978-1-4939-6824-4\\_22](https://doi.org/10.1007/978-1-4939-6824-4_22)
- Durant, J., Leland, B., Henry, D., et al. (2002). Reoptimization of MDL keys for use in drug discovery. *Journal of Chemical Information and Computer Sciences*, 42(6), 1273–1280. <https://doi.org/10.1021/CI010132R>
- Dykens, J. A., Jamieson, J. D., Marroquin, L. D., et al. (2008). In vitro assessment of mitochondrial dysfunction and cytotoxicity of nefazodone, trazodone, and buspirone. *Toxicological Sciences*, 103(2), 335–245. <https://doi.org/10.1093/toxsci/kfn056>

- Dykens, J. A., Marroquin, L. D., & Will, Y. (2007). Strategies to reduce late-stage drug attrition due to mitochondrial toxicity. In *Expert Review of Molecular Diagnostics* (Vol. 7, Issue 2, pp. 161–175). *Expert Rev Mol Diagn*. <https://doi.org/10.1586/14737159.7.2.161>
- Dykens, J. A., & Will, Y. (2007). The significance of mitochondrial toxicity testing in drug development. *Drug Discovery Today*, 12(17–18), 777–785. <https://doi.org/10.1016/j.drudis.2007.07.013>
- Dykens, J. A., & Will, Y. (2008). Drug-Induced Mitochondrial Dysfunction. *Drug-Induced Mitochondrial Dysfunction*, 1–616. <https://doi.org/10.1002/9780470372531>
- Eakins, J., Bauch, C., Woodhouse, H., et al. (2016). A combined in vitro approach to improve the prediction of mitochondrial toxicants. *Toxicology in Vitro*, 34, 161–170. <https://doi.org/10.1016/j.tiv.2016.03.016>
- Eden, E., Navon, R., Steinfeld, I., et al. (2009). GOrilla: A tool for discovery and visualization of enriched GO terms in ranked gene lists. *BMC Bioinformatics*, 10, 48. <https://doi.org/10.1186/1471-2105-10-48>
- Efendiev, M. A., Otani, M., & Eberl, H. J. (2020). Mathematical Analysis of a PDE-ODE Coupled Model of Mitochondrial Swelling with Degenerate Calcium Ion Diffusion. *Society for Industrial and Applied Mathematics*, 52(1), 543–569. <https://doi.org/10.1137/18M1227421>
- EFSA (2018) Benford D, Halldorsson T, Jeger MJ, Knutsen HK, More S, Naegeli H, Noteborn H, Ockleford C, Ricci A, Rychen G, Schlatter JR, Silano V, Solecki R, Turck D, Younes M, Craig P, Hart A, Von Goetz N, Koutsoumanis K, Mortensen A, Ossendorp B, Martino L, Merten C, Mosbach-Schulz O and Hardy A, 2018. Guidance on Uncertainty Analysis in Scientific Assessments. *EFSA Journal* 2018;16(1):5123, 39 pp <https://doi.org/10.2903/j.efsa.2018.5123>
- Ehse, S., Raschke, I., Mancuso, G., et al. (2009). Regulation of OPA1 processing and mitochondrial fusion by m-AAA protease isoenzymes and OMA1. *Journal of Cell Biology*, 187(7), 1023–1036. <https://doi.org/10.1083/jcb.200906084>
- Else, A. J., Barnes, S. J., Danson, M. J., et al. (1988). A new spectrophotometric assay for citrate synthase and its use to assess the inhibitory effects of palmitoyl thioesters. *Biochemical Journal*, 251(3), 803–807. <https://doi.org/10.1042/bj2510803>
- Emwas, A. H. M. (2015). The strengths and weaknesses of NMR spectroscopy and mass spectrometry with particular focus on metabolomics research. *Methods in Molecular Biology*, 1277, 161–193. [https://doi.org/10.1007/978-1-4939-2377-9\\_13](https://doi.org/10.1007/978-1-4939-2377-9_13)
- Escher, S., Kamp, H., Bennekou, S., et al. (2019). Towards grouping concepts based on new approach methodologies in chemical hazard assessment: the read-across approach of the EU-ToxRisk project. *Archives of Toxicology*, 93(12), 3643–3667. <https://doi.org/10.1007/S00204-019-02591-7>
- Eskelinen, E. L., Reggiori, F., Baba, M., et al. (2011). Seeing is believing: The impact of electron microscopy on autophagy research. In *Autophagy* (Vol. 7, Issue 9, pp. 935–956). Taylor and Francis Inc. <https://doi.org/10.4161/auto.7.9.15760>
- Esser, L., Quinn, B., Li, Y., et al. (2004). Crystallographic studies of quinol oxidation site inhibitors: a modified classification of inhibitors for the cytochrome bc(1) complex. *Journal of Molecular Biology*, 341(1), 281–302. <https://doi.org/10.1016/J.JMB.2004.05.065>
- Esser, L., Yu, C., & Xia, D. (2014). Structural basis of resistance to anti-cytochrome bc<sub>1</sub> complex inhibitors: implication for drug improvement. *Current Pharmaceutical Design*, 20(5), 704–724. <https://doi.org/10.2174/138161282005140214163327>
- Esterhuizen, K., van der Westhuizen, F. H., & Louw, R. (2017). Metabolomics of mitochondrial disease. In *Mitochondrion* (Vol. 35, pp. 97–110). <https://doi.org/10.1016/j.mito.2017.05.012>
- EU Scientific advice mechanism (2018) EU Authorisation Processes of Plant Protection Products – From a Scientific Point of View. Publications Office of the EU, Luxembourg. <https://doi.org/10.2777/238919>
- European Commission, Joint Research Centre (JRC) (2019): EURL ECVAM dataset on alternative methods to animal experimentation (DB-ALM). PID: <http://data.europa.eu/89h/b7597ada-148d-4560-9079-ab0a5539cad3>
- European committee (2006) Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), establishing a European Chemicals Agency, amending Directive 1999/45/EC and repealing Council Regulation (EEC) No 793/93 and Commission Regulation (EC) No 1488/94 as well as Council Directive 76/769/EEC and Commission Directives 91/155/EEC, 93/67/EEC, 93/105/EC and 2000/21/EC, <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32006R1907>
- European committee (2009) Regulation (EC) No 1223/2009 of the European Parliament and of the Council of 30 November 2009 on cosmetic products (recast) <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:02009R1223-20190813> (found via: [https://ec.europa.eu/growth/sectors/cosmetics/animal-testing\\_en](https://ec.europa.eu/growth/sectors/cosmetics/animal-testing_en))
- European Parliament and the council (2009), Regulation (EC) No 1107/2009 of the European Parliament and of the Council of 21 October 2009 concerning the placing of plant protection products on the market and repealing Council Directives 79/117/EEC and 91/414/EEC (OJ L 309, 24.11.2009, p. 1) <http://data.europa.eu/eli/reg/2009/1107/oj>
- European Parliament and the council (2020) Evaluation of Regulation (EC) No 1107/2009 on the placing of plant protection products on the market and of Regulation (EC) No 396/2005 on maximum residue levels of pesticides. Brussels <https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52020DC0208&from=EN>
- Fahrner, J. A., Liu, R., Perry, M. S., et al. (2016). A novel de novo dominant negative mutation in DNML1 impairs mitochondrial fission and presents as childhood epileptic encephalopathy. *American Journal of Medical Genetics, Part A*, 170(8), 2002–2011. <https://doi.org/10.1002/ajmg.a.37721>
- Fazzini, F., Schöpf, B., Blatzer, M., et al. (2018). Plasmid-normalized quantification of relative mitochondrial DNA copy number. *Scientific Reports*, 8(1). <https://doi.org/10.1038/s41598-018-33684-5>



- Felser, A., Blum, K., Lindinger, P. W., et al. (2013). Mechanisms of hepatocellular toxicity associated with dronedarone - A comparison to amiodarone. *Toxicological Sciences*, 131(2), 480–490. <https://doi.org/10.1093/toxsci/kfs298>
- Felser, A., Lindinger, P. W., Schnell, D., et al. (2014). Hepatocellular toxicity of benzobromarone: Effects on mitochondrial function and structure. *Toxicology*, 324, 136–146. <https://doi.org/10.1016/j.tox.2014.08.002>
- Fernandes, J., Chandler, J. D., Lili, L. N., et al. (2019). Transcriptome analysis reveals distinct responses to physiologic versus toxic manganese exposure in human neuroblastoma cells. In *Frontiers in Genetics* (Vol. 10, p. 676). <https://doi.org/10.3389/fgene.2019.00676>
- Fernandez-Fernandez, S., Almeida, A., & Bolaños, J. P. (2012). Antioxidant and bioenergetic coupling between neurons and astrocytes. *Biochemical Journal*, 443(1), 3–11. <https://doi.org/10.1042/BJ20111943>
- Ferrick, D. A., Neilson, A., & Beeson, C. (2008). Advances in measuring cellular bioenergetics using extracellular flux. In *Drug Discovery Today* (Vol. 13, Issues 5–6, pp. 268–274). *Drug Discov Today*. <https://doi.org/10.1016/j.drudis.2007.12.008>
- Fischer, C. A., Besora-Casals, L., Rolland, S. G., et al. (2020). MitoSegNet: Easy-to-use Deep Learning Segmentation for Analyzing Mitochondrial Morphology. *iScience*, 23(10), 101601. <https://doi.org/10.1016/j.isci.2020.101601>
- Fisher, C., Siméon, S., Jamei, M., et al. (2019). VIVD: Virtual in vitro distribution model for the mechanistic prediction of intracellular concentrations of chemicals in in vitro toxicity assays. *Toxicology in Vitro*, 58, 42–50. <https://doi.org/10.1016/j.tiv.2018.12.017>
- Florez-Sarasa, I., Ribas-Carbo, M., Del-Saz, N. F., et al. (2016). Unravelling the in vivo regulation and metabolic role of the alternative oxidase pathway in C3 species under photoinhibitory conditions. *The New Phytologist*, 212(1), 66–79. <https://doi.org/10.1111/nph.14030>
- Fonteriz, R. I., de la Fuente, S., Moreno, A., et al. (2010). Monitoring mitochondrial [Ca<sup>2+</sup>] dynamics with rhod-2, ratiometric pericam and aequorin. *Cell Calcium*, 48(1), 61–69. <https://doi.org/10.1016/j.ceca.2010.07.001>
- Foran, C. M., Rycroft, T., Keisler, J., et al. (2019). A modular approach for assembly of quantitative adverse outcome pathways. *Altex*, 36(3), 353–362. <https://doi.org/10.14573/altex.1810181>
- Forred, B. J., Daugaard, D. R., Titus, B. K., et al. (2017). Detoxification of mitochondrial oxidants and apoptotic signaling are facilitated by thioredoxin-2 and peroxiredoxin-3 during hyperoxic injury. *PLoS ONE*, 12(1), e0168777. <https://doi.org/10.1371/journal.pone.0168777>
- Friedman, J. R., & Nunnari, J. (2014). Mitochondrial form and function. *Nature*, 505(7483), 335–343. <https://doi.org/10.1038/nature12985>
- Fröhlich, F., Theis, F. J., & Hasenauer, J. (2014). Uncertainty analysis for non-identifiable dynamical systems: Profile likelihoods, bootstrapping and more. *Lecture Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics)*, 8859, 61–72. [https://doi.org/10.1007/978-3-319-12982-2\\_5](https://doi.org/10.1007/978-3-319-12982-2_5)
- From, A. H. L., & Ugurbil, K. (2011). Standard magnetic resonance-based measurements of the pi(ATP) rate do not index the rate of oxidative phosphorylation in cardiac and skeletal muscles. *American Journal of Physiology - Cell Physiology*, 301(1). <https://doi.org/10.1152/ajpcell.00345.2010>
- Fromenty, B. (2019). Inhibition of mitochondrial fatty acid oxidation in drug-induced hepatic steatosis. In *Liver Research* (Vol. 3, Issues 3–4, pp. 157–169). <https://doi.org/10.1016/j.livres.2019.06.001>
- Gan, C.-S., Chong, P. K., Pham, T. K., et al. (2007). Technical, experimental, and biological variations in isobaric tags for relative and absolute quantitation (iTRAQ). *Journal of Proteome Research*, 6(2), 821–827. <https://doi.org/10.1021/pr060474i>
- Gao, X., Wen, X., Esser, L., et al. (2003). Structural basis for the quinone reduction in the bc1 complex: a comparative analysis of crystal structures of mitochondrial cytochrome bc1 with bound substrate and inhibitors at the Qi site. *Biochemistry*, 42(30), 9067–9080. <https://doi.org/10.1021/BIO341814>
- Garaschuk, O., Griesbeck, O., & Konnerth, A. (2007). Troponin C-based biosensors: A new family of genetically encoded indicators for in vivo calcium imaging in the nervous system. In *Cell Calcium* (Vol. 42, Issues 4–5, pp. 351–361). Elsevier Ltd. <https://doi.org/10.1016/j.ceca.2007.02.011>
- Garcia-Alonso, L., Ibrahim, M., Turei, D., et al. (2018). Benchmark and integration of resources for the estimation of human transcription factor activities. *Genome Res.*, 29(8), 1363–1375. <https://doi.org/10.1101/337915>
- Garrido, C., Galluzzi, L., Brunet, M., et al. (2006). Mechanisms of cytochrome c release from mitochondria. *Cell Death and Differentiation*, 13, 1423–1433. <https://doi.org/10.1038/sj.cdd.4401950>
- Gautier, L., Cope, L., Bolstad, B. M., et al. (2004). Affy - Analysis of Affymetrix GeneChip data at the probe level. *Bioinformatics*, 20(3), 307–315. <https://doi.org/10.1093/bioinformatics/btg405>
- Gawlowski, T., Suarez, J., Scott, B., et al. (2012). Modulation of dynamin-related protein 1 (DRP1) function by increased O-linked-β-N-acetylglucosamine modification (O-GlcNAc) in cardiac myocytes. *Journal of Biological Chemistry*, 287(35), 30024–30034. <https://doi.org/10.1074/jbc.M112.390682>
- Geiger, T., Wisniewski, J. R., Cox, J., et al. (2011). Use of stable isotope labeling by amino acids in cell culture as a spike-in standard in quantitative proteomics. *Nature Protocols*, 6(2), 147–157. <https://doi.org/10.1038/nprot.2010.192>
- Georgakopoulos, N. D., Wells, G., & Campanella, M. (2017). The pharmacological regulation of cellular mitophagy. In *Nature Chemical Biology* (Vol. 13, Issue 2, pp. 136–146). <https://doi.org/10.1038/nchembio.2287>
- Gerencser, A. A., Neilson, A., Choi, S. W., et al. (2009). Quantitative microplate-based respirometry with correction for oxygen diffusion. *Analytical Chemistry*, 81(16), 6868–6878. <https://doi.org/10.1021/ac900881z>
- Gerets, H. H. J., Tilmant, K., Gerin, B., et al. (2012). Characterization of primary human hepatocytes, HepG2 cells, and HepaRG cells at the mRNA level and CYP activity in response to inducers and their predictivity for the detection of human hepatotoxins. *Cell Biology and Toxicology*, 28(2), 69–87. <https://doi.org/10.1007/s10565-011-9208-4>

- Ghezzi, D., Arzuffi, P., Zordan, M., et al. (2011). Mutations in TTC19 cause mitochondrial complex III deficiency and neurological impairment in humans and flies. *Nature Genetics*, 43(3), 259–263. <https://doi.org/10.1038/NG.761>
- Ghosh, R., Goswami, S. K., Feitoza, L. F. B. B., et al. (2016). Diclofenac induces proteasome and mitochondrial dysfunction in murine cardiomyocytes and hearts. *International Journal of Cardiology*, 223, 923–935. <https://doi.org/10.1016/j.ijcard.2016.08.233>
- Giacomello, M., Pyakurel, A., Glytsou, C., et al. (2020). The cell biology of mitochondrial membrane dynamics. *Nature Reviews Molecular Cell Biology*, 21(4), 204–224. <https://doi.org/10.1038/s41580-020-0210-7>
- Giedt, R. J., Fumene Feruglio, P., Pathania, D., et al. (2016). Computational imaging reveals mitochondrial morphology as a biomarker of cancer phenotype and drug response. *Scientific Reports*, 6, 32985. <https://doi.org/10.1038/srep32985>
- Giglia-Mari, G., Zotter, A., & Vermeulen, W. (2011). DNA damage response. *Cold Spring Harbor Perspectives in Biology*, 3(1), a000745. <https://doi.org/10.1101/cshperspect.a000745>
- Gijbels, E., Vilas-Boas, V., Annaert, P., et al. (2020). Robustness testing and optimization of an adverse outcome pathway on cholestatic liver injury. *Archives of Toxicology*, 94(4), 1151–1172. <https://doi.org/10.1007/s00204-020-02691-9>
- Giorgi, C., Agnoletto, C., Bononi, A., et al. (2012). Mitochondrial calcium homeostasis as potential target for mitochondrial medicine. In *Mitochondrion* (Vol. 12, Issue 1, pp. 77–85). <https://doi.org/10.1016/j.mito.2011.07.004>
- Giorgi, C., Marchi, S., & Pinton, P. (2018). The machineries, regulation and cellular functions of mitochondrial calcium. In *Nature Reviews Molecular Cell Biology* (Vol. 19, Issue 11, pp. 713–730). <https://doi.org/10.1038/s41580-018-0052-8>
- Gomes, S. I. L., Roca, C. P., Scott-Fordsmand, J. J., et al. (2019). High-throughput transcriptomics: Insights into the pathways involved in (nano) nickel toxicity in a key invertebrate test species. *Environmental Pollution*, 245, 131–140. <https://doi.org/10.1016/j.envpol.2018.10.123>
- Gong, Z., Tas, E., & Muzumdar, R. (2014). Humanin and age-related diseases: A new link? *Frontiers in Endocrinology*, 5, 210. <https://doi.org/10.3389/fendo.2014.00210>
- Gonzalez-Coloma, A., Reina, M., Diaz, C. E., et al. (2013). Natural Product-Based Biopesticides for Insect Control. In *Reference Module in Chemistry, Molecular Sciences and Chemical Engineering*. Elsevier. <https://doi.org/10.1016/B978-0-12-409547-2.02770-0>
- Goodwin, W. H. (2015). DNA: Mitochondrial DNA. In *Encyclopedia of Forensic and Legal Medicine: Second Edition* (pp. 351–358). Elsevier Inc. <https://doi.org/10.1016/B978-0-12-800034-2.00155-5>
- Görlach, A., Bertram, K., Hudecova, S., et al. (2015). Calcium and ROS: A mutual interplay. In *Redox Biology* (Vol. 6, pp. 260–271). <https://doi.org/10.1016/j.redox.2015.08.010>
- Govindan, S., Batti, L., Osterop, S. F., et al. (2021). Mass Generation, Neuron Labeling, and 3D Imaging of Minibrains. *Frontiers in Bioengineering and Biotechnology*, 8, 1436. <https://doi.org/10.3389/fbioe.2020.582650>
- Grandl, M., & Schmitz, G. (2010). Fluorescent high-content imaging allows the discrimination and quantitation of E-LDL-induced lipid droplets and Ox-LDL-generated phospholipidosis in human macrophages. *Cytometry Part A*, 77(3), 231–242. <https://doi.org/10.1002/cyto.a.20828>
- Griesbeck, O., Baird, G. S., Campbell, R. E., et al. (2001). Reducing the environmental sensitivity of yellow fluorescent protein. Mechanism and applications. *Journal of Biological Chemistry*, 276(31), 29188–29194. <https://doi.org/10.1074/jbc.M102815200>
- Grohm, J., Kim, S. W., Mamrak, U., et al. (2012). Inhibition of Drp1 provides neuroprotection in vitro and in vivo. *Cell Death and Differentiation*, 19(9), 1446–1458. <https://doi.org/10.1038/cdd.2012.18>
- Grüning, D., Felsner, A., Bouitbir, J., et al. (2017). The catechol-O-methyltransferase inhibitors tolcapone and entacapone uncouple and inhibit the mitochondrial respiratory chain in HepaRG cells. *Toxicology in Vitro*, 42, 337–347. <https://doi.org/10.1016/j.tiv.2017.05.013>
- Grynkiewicz, G., Poenie, M., & Tsien, R. Y. (1985). A new generation of Ca<sup>2+</sup> indicators with greatly improved fluorescence properties. In *Journal of Biological Chemistry* (Vol. 260, Issue 6, pp. 3440–3450). Elsevier. [https://doi.org/10.1016/s0021-9258\(19\)83641-4](https://doi.org/10.1016/s0021-9258(19)83641-4)
- Gu, X., & Manautou, J. E. (2012). Molecular mechanisms underlying chemical liver injury. In *Expert Reviews in Molecular Medicine* (Vol. 14, p. e4). <https://doi.org/10.1017/S1462399411002110>
- Gugiatti, E., Tenca, C., Ravera, S., et al. (2018). A reversible carnitine palmitoyltransferase (CPT1) inhibitor offsets the proliferation of chronic lymphocytic leukemia cells. In *Haematologica* (Vol. 103, Issue 11, pp. e531–e536). <https://doi.org/10.3324/haematol.2017.175414>
- Guo, J., Nguyen, H. T., Ito, S., et al. (2018). In ovo exposure to triclosan alters the hepatic proteome in chicken embryos. *Ecotoxicology and Environmental Safety*, 165, 495–504. <https://doi.org/10.1016/j.ecoenv.2018.09.043>
- Haber, L. T., Dourson, M. L., Allen, B. C., et al. (2018). Benchmark dose (BMD) modeling: current practice, issues, and challenges. In *Critical Reviews in Toxicology* (Vol. 48, Issue 5, pp. 387–415). <https://doi.org/10.1080/10408444.2018.1430121>
- Halestrap, A. P. (2009). What is the mitochondrial permeability transition pore? In *Journal of Molecular and Cellular Cardiology* (Vol. 46, Issue 6, pp. 821–831). <https://doi.org/10.1016/j.yjmcc.2009.02.021>
- Halevy, R., Shtirberg, L., Shklyar, M., et al. (2010). Electron spin resonance micro-imaging of live species for oxygen mapping. *Journal of Visualized Experiments*, 42, 2122. <https://doi.org/10.3791/2122>
- Hallinger, D. R., Lindsay, H. B., Friedman, K. P., et al. (2020). Respirometric screening and characterization of mitochondrial toxicants within the toxcast phase I and II chemical libraries. *Toxicological Sciences*, 176(1), 715–192. <https://doi.org/10.1093/toxsci/kfaa059>

- Hamacher-Brady, A., & Brady, N. R. (2016). Mitophagy programs: Mechanisms and physiological implications of mitochondrial targeting by autophagy. In *Cellular and Molecular Life Sciences* (Vol. 73, Issue 4, pp. 775–795). <https://doi.org/10.1007/s00018-015-2087-8>
- Hammerling, B. C., Najor, R. H., Cortez, M. Q., et al. (2017). A Rab5 endosomal pathway mediates Parkin-dependent mitochondrial clearance. *Nature Communications*, 8, 14050. <https://doi.org/10.1038/ncomms14050>
- Han, D., Dara, L., Win, S., et al. (2013). Regulation of drug-induced liver injury by signal transduction pathways: Critical role of mitochondria. In *Trends in Pharmacological Sciences* (Vol. 34, Issue 4, pp. 243–253). <https://doi.org/10.1016/j.tips.2013.01.009>
- Harder, Z., Zunino, R., & McBride, H. (2004). Sumo1 Conjugates Mitochondrial Substrates and Participates in Mitochondrial Fission. *Current Biology*, 14(4), 340–345. <https://doi.org/10.1016/j.cub.2004.02.004>
- Harris, G., Eschment, M., Orozco, S. P., et al. (2018). Toxicity, recovery, and resilience in a 3D dopaminergic neuronal in vitro model exposed to rotenone. *Archives of Toxicology*, 92(8), 2587–2606. <https://doi.org/10.1007/s00204-018-2250-8>
- Hartung, T. (2016). Making big sense from big data in toxicology by read-across. *Altex*, 33(2), 83–93. <https://doi.org/10.14573/altex.1603091>
- Harwig, M. C., Viana, M. P., Egner, J. M., et al. (2018). Methods for imaging mammalian mitochondrial morphology: A prospective on MitoGraph. *Analytical Biochemistry*, 552, 81–99. <https://doi.org/10.1016/j.ab.2018.02.022>
- Head, B., Griparic, L., Amiri, M., et al. (2009). Inducible proteolytic inactivation of OPA1 mediated by the OMA1 protease in mammalian cells. *Journal of Cell Biology*, 187(7), 959–966. <https://doi.org/10.1083/jcb.200906083>
- Heijne, W. H. M., Kienhuis, A. S., Van Ommen, B., et al. (2005). Systems toxicology: Applications of toxicogenomics, transcriptomics, proteomics and metabolomics in toxicology. In *Expert Review of Proteomics* (Vol. 2, Issue 5, pp. 767–780). <https://doi.org/10.1586/14789450.2.5.767>
- Heim, N., & Griesbeck, O. (2004). Genetically Encoded Indicators of Cellular Calcium Dynamics Based on Troponin C and Green Fluorescent Protein. *Journal of Biological Chemistry*, 279(14), 14280–14286. <https://doi.org/10.1074/jbc.M312751200>
- Heinonen, S., Buzkova, J., Muniandy, M., et al. (2015). Impaired mitochondrial biogenesis in adipose tissue in acquired obesity. *Diabetes*, 64(9), 3135–3145. <https://doi.org/10.2337/db14-1937>
- Hemmerich, J., Troger, F., Füzi, B., et al. (2020). Using Machine Learning Methods and Structural Alerts for Prediction of Mitochondrial Toxicity. *Molecular Informatics*, 39(5), e2000005. <https://doi.org/10.1002/minf.202000005>
- Hetz, C. (2012). The unfolded protein response: Controlling cell fate decisions under ER stress and beyond. In *Nature Reviews Molecular Cell Biology* (Vol. 13, Issue 2, pp. 89–102). <https://doi.org/10.1038/nrm3270>
- Hiemstra, S., Ramaiahgari, S., Wink, S., et al. (2019). High-throughput confocal imaging of differentiated 3D liver-like spheroid cellular stress response reporters for identification of drug-induced liver injury liability. *Archives of Toxicology*, 93(10), 2895–2911. <https://doi.org/10.1007/S00204-019-02552-0>
- Hock, M. B., & Kralli, A. (2009). Transcriptional Control of Mitochondrial Biogenesis and Function. *Annual Review of Physiology*, 71, 177–2023. <https://doi.org/10.1146/annurev.physiol.010908.163119>
- Hodneland Nilsson, L. I., Nitschke Pettersen, I. K., Nikolaisen, J., et al. (2015). A new live-cell reporter strategy to simultaneously monitor mitochondrial biogenesis and morphology. *Scientific Reports*, 5. <https://doi.org/10.1038/srep17217>
- Holley, A. K., Bakthavatchalu, V., Velez-Roman, J. M., et al. (2011). Manganese superoxide dismutase: Guardian of the powerhouse. In *International Journal of Molecular Sciences* (Vol. 12, Issue 10, pp. 7114–7162). <https://doi.org/10.3390/ijms12107114>
- Hong, S., & Pedersen, P. L. (2008). ATP Synthase and the Actions of Inhibitors Utilized To Study Its Roles in Human Health, Disease, and Other Scientific Areas. *Microbiology and Molecular Biology Reviews*, 72(4), 590–641. <https://doi.org/10.1128/mmr.00016-08>
- Horsefield, R., Yankovskaya, V., Sexton, G., et al. (2006). Structural and computational analysis of the quinone-binding site of complex II (succinate-ubiquinone oxidoreductase): a mechanism of electron transfer and proton conduction during ubiquinone reduction. *The Journal of Biological Chemistry*, 281(11), 7309–7316. <https://doi.org/10.1074/JBC.M508173200>
- Hothorn, T., Bretz, F., & Westfall, P. (2008). Simultaneous inference in general parametric models. *Biometrical Journal. Biometrische Zeitschrift*, 50(3), 346–363. <https://doi.org/10.1002/BIMJ.200810425>
- Hsieh, A. Y. Y., Budd, M., Deng, D., et al. (2018). A Monochrome Multiplex Real-Time Quantitative PCR Assay for the Measurement of Mitochondrial DNA Content. *Journal of Molecular Diagnostics*, 20(5), 612–620. <https://doi.org/10.1016/j.jmoldx.2018.05.001>
- Huang, L., Sun, G., Cobessi, D., et al. (2006). 3-nitropropionic acid is a suicide inhibitor of mitochondrial respiration that, upon oxidation by complex II, forms a covalent adduct with a catalytic base arginine in the active site of the enzyme. *The Journal of Biological Chemistry*, 281(9), 5965–5972. <https://doi.org/10.1074/JBC.M511270200>
- Huber, W., von Heydebreck, A., Suelmann, H., Poustka, A., Vingron, M., (2002) Variance Stabilization Applied to Microarray Data Calibration and to the Quantification of Differential Expression. *Bioinformatics* 18, S96–S104, <https://bioconductor.org/packages/release/bioc/html/vsn.html>
- Huizing, M., Ruitenbeek, W., Thinnies, F. P., et al. (1996). Deficiency of the voltage-dependent anion channel: A novel cause of mitochondriopathy. *Pediatric Research*, 39(5), 760–765. <https://doi.org/10.1203/00006450-199605000-00003>
- Huynh, F. K., Green, M. F., Koves, T. R., et al. (2014). Measurement of fatty acid oxidation rates in animal tissues and cell lines. In *Methods in Enzymology* (Vol. 542, pp. 391–405). Academic Press Inc. <https://doi.org/10.1016/B978-0-12-416618-9.00020-0>
- Hwang, B., Lee, J. H., & Bang, D. (2018). Single-cell RNA sequencing technologies and bioinformatics pipelines. In *Experimental and Molecular Medicine* (Vol. 50, Issue 8, p. 96). Nature Publishing Group. <https://doi.org/10.1038/s12276-018-0071-8>

- Hwang, R. Der, Wiemerslage, L., LaBreck, C. J., et al. (2014). The neuroprotective effect of human uncoupling protein 2 (hUCP2) requires cAMP-dependent protein kinase in a toxin model of Parkinson's disease. *Neurobiology of Disease*, 69, 180–191. <https://doi.org/10.1016/j.nbd.2014.05.032>
- Hynes, J., Floyd, S., Soini, A. E., et al. (2003). Fluorescence-based cell viability screening assays using water-soluble oxygen probes. *Journal of Biomolecular Screening*, 8(3), 264–272. <https://doi.org/10.1177/1087057103008003004>
- Hynes, J., Marroquin, L. D., Ogurtsov, V. I., et al. (2006). Investigation of drug-induced mitochondrial toxicity using fluorescence-based oxygen-sensitive probes. *Toxicological Sciences*, 92(1), 186–200. <https://doi.org/10.1093/toxsci/kfj208>
- Igarashi, Y., Nakatsu, N., Yamashita, T., et al. (2015). Open TG-GATEs: A large-scale toxicogenomics database. *Nucleic Acids Research*, 43, D921–D927. <https://doi.org/10.1093/nar/gku955>
- Ikuhiro, K., Paul, K. M., & Hyder, F. (2004). Dynamic Imaging of Perfusion and Oxygenation by Functional Magnetic Resonance Imaging. *Journal of Cerebral Blood Flow & Metabolism*, 24(12), 1369–1381. <https://doi.org/10.1097/01.wcb.0000141501.12558.9b>
- Imamura, H., Huynh Nhat, K. P., Togawa, H., et al. (2009). Visualization of ATP levels inside single living cells with fluorescence resonance energy transfer-based genetically encoded indicators. *Proceedings of the National Academy of Sciences of the United States of America*, 106(37), 15651–15656. <https://doi.org/10.1073/pnas.0904764106>
- Indiveri, C., Iacobazzi, V., Tonazzi, A., et al. (2011). The mitochondrial carnitine/acylcarnitine carrier: Function, structure and physiopathology. *Molecular Aspects of Medicine*, 32(4–6), 223–233. <https://doi.org/10.1016/j.mam.2011.10.008>
- Inouye, S., & Tsuji, F. I. (1993). Cloning and sequence analysis of cDNA for the Ca<sup>2+</sup>-activated photoprotein, clytin. *FEBS Letters*, 315(3), 343–346. [https://doi.org/10.1016/0014-5793\(93\)81191-2](https://doi.org/10.1016/0014-5793(93)81191-2)
- Irobi, J., Holmgren, A., Winter, V. De, et al. (2012). Mutant HSPB8 causes protein aggregates and a reduced mitochondrial membrane potential in dermal fibroblasts from distal hereditary motor neuropathy patients. *Neuromuscular Disorders*, 22(8), 699–711. <https://doi.org/10.1016/j.nmd.2012.04.005>
- Ishikawa, K., Yoshida, K., Kanie, K., et al. (2019). Morphology-Based Analysis of Myoblasts for Prediction of Myotube Formation. *SLAS Discovery*, 24(1), 47–56. <https://doi.org/10.1177/2472555218793374>
- Jacobs, L. J. A. M., de Wert, G., Geraedts, J. P. M., et al. (2006). The transmission of OXPHOS disease and methods to prevent this. In *Human Reproduction Update* (Vol. 12, Issue 2, pp. 119–136). <https://doi.org/10.1093/humupd/dmi042>
- Jafarian, V., Sariri, R., Hosseinkhani, S., et al. (2011). A unique EF-hand motif in mnmiepsin photoprotein from *Mnemioepis leidy*: Implication for its low calcium sensitivity. *Biochemical and Biophysical Research Communications*, 413(2), 164–170. <https://doi.org/10.1016/j.bbrc.2011.08.022>
- Jahani-Asl, A., & Slack, R. S. (2007). The phosphorylation state of Drp1 determines cell fate. In *EMBO Reports* (Vol. 8, Issue 10, pp. 912–913). <https://doi.org/10.1038/sj.embor.7401077>
- Jarabek, A. M., & Hines, D. E. (2019). Mechanistic integration of exposure and effects: advances to apply systems toxicology in support of regulatory decision-making. In *Current Opinion in Toxicology* (Vol. 16, pp. 83–92). Elsevier B.V. <https://doi.org/10.1016/j.cotox.2019.09.001>
- Jassal, B., Matthews, L., Viteri, G., et al. (2020). The reactome pathway knowledgebase. *Nucleic Acids Research*, 48(D1), D498–D503. <https://doi.org/10.1093/nar/gkz1031>
- Jennings, P., Koppelstaetter, C., Aydin, S., et al. (2007). Cyclosporin A induces senescence in renal tubular epithelial cells. *American Journal of Physiology - Renal Physiology*, 293(3), F831–F838. <https://doi.org/10.1152/ajprenal.00005.2007>
- Jennings, P., Koppelstaetter, C., Pfaller, W., et al. (2004). Assessment of a new cell culture perfusion apparatus for in vitro chronic toxicity testing part 1: Technical description. *Altex*, 21(2), 51–60.
- Johansson, H. K. L., Svingen, T., Boberg, J., et al. (2020). Calretinin is a novel candidate marker for adverse ovarian effects of early life exposure to mixtures of endocrine disruptors in the rat. *Archives of Toxicology*, 94(9), 1241–1250. <https://doi.org/10.1007/s00204-020-02697-3>
- Johnson, J., Walsh, M., Bockus, B., et al. (1981). Monitoring of relative mitochondrial membrane potential in living cells by fluorescence microscopy. *The Journal of Cell Biology*, 88(3), 526–535. <https://doi.org/10.1083/JCB.88.3.526>
- Johnson, J., Walsh, M., & Chen, L. (1980). Localization of mitochondria in living cells with rhodamine 123. *Proc Nat Acad Sci USA*, 77(2), 990–994. <https://doi.org/10.1073/PNAS.77.2.990>
- Jones, A. J. Y., & Hirst, J. (2013). A spectrophotometric coupled enzyme assay to measure the activity of succinate dehydrogenase. *Analytical Biochemistry*, 442(1), 19–23. <https://doi.org/10.1016/j.ab.2013.07.018>
- Jones, E., Gaytan, N., Garcia, I., et al. (2017). A threshold of transmembrane potential is required for mitochondrial dynamic balance mediated by DRP1 and OMA1. *Cellular and Molecular Life Sciences*, 74(7), 1347–1363. <https://doi.org/10.1007/s00018-016-2421-9>
- Jornayvaz, F. R., & Shulman, G. I. (2010). Regulation of mitochondrial biogenesis. *Essays in Biochemistry*, 47, 69–84. <https://doi.org/10.1042/BSE0470069>
- Joseph, P. (2017). Transcriptomics in toxicology. *Food and Chemical Toxicology*, 109, 650–662. <https://doi.org/10.1016/j.fct.2017.07.031>
- Jourdain, A., & Martinou, J. C. (2010). Mitochondrial dynamics: Quantifying mitochondrial fusion in vitro. *BMC Biology*, 8, 99. <https://doi.org/10.1186/1741-7007-8-99>
- Jovaisaite, V., & Auwerx, J. (2015). The mitochondrial unfolded protein response-synchronizing genomes. In *Current Opinion in Cell Biology* (Vol. 33, pp. 74–81). <https://doi.org/10.1016/j.ccb.2014.12.003>

- Kamalian, L., Chadwick, A. E., Bayliss, M., et al. (2015). The utility of HepG2 cells to identify direct mitochondrial dysfunction in the absence of cell death. *Toxicology in Vitro*, 29(4), 732–740. <https://doi.org/10.1016/j.tiv.2015.02.011>
- Kamentsky, L., Jones, T. R., Fraser, A., et al. (2011). Improved structure, function and compatibility for cellprofiler: Modular high-throughput image analysis software. *Bioinformatics*, 27(8), 1179–1180. <https://doi.org/10.1093/bioinformatics/btr095>
- Kanehisa, M., & Goto, S. (2000). KEGG: Kyoto Encyclopedia of Genes and Genomes. In *Nucleic Acids Research* (Vol. 28, Issue 1, pp. 27–30). <https://doi.org/10.1093/nar/28.1.27>
- Karbowski, M., Cleland, M. M., & Roelofs, B. A. (2014). Photoactivatable green fluorescent protein-based visualization and quantification of mitochondrial fusion and mitochondrial network complexity in living cells. In *Methods in Enzymology* (Vol. 547, Issue C, pp. 57–73). Academic Press Inc. <https://doi.org/10.1016/B978-0-12-801415-8.00004-7>
- Kaspar, S., Oertlin, C., Szczepanowska, K., et al. (2021). Adaptation to mitochondrial stress requires CHOP-directed tuning of ISR. *Science Advances*, 7(22), eabf0971. <https://doi.org/10.1126/SCIADV.ABF0971>
- Katayama, H., Kogure, T., Mizushima, N., et al. (2011). A sensitive and quantitative technique for detecting autophagic events based on lysosomal delivery. *Chemistry and Biology*, 18(8), 1042–1052. <https://doi.org/10.1016/j.chembiol.2011.05.013>
- Kaufmann, P., Török, M., Hänni, A., et al. (2005). Mechanisms of benzarone and benzbromarone-induced hepatic toxicity. *Hepatology*, 41(4), 925–935. <https://doi.org/10.1002/hep.20634>
- Kennedy, A. S., Raleigh, J. A., Perez, G. M., et al. (1997). Proliferation and hypoxia in human squamous cell carcinoma of the cervix: First report of combined immunohistochemical assays. *International Journal of Radiation Oncology Biology Physics*, 37(4), 897–905. [https://doi.org/10.1016/S0360-3016\(96\)00539-1](https://doi.org/10.1016/S0360-3016(96)00539-1)
- Kennedy, S. (2002). The role of proteomics in toxicology: Identification of biomarkers of toxicity by protein expression analysis. In *Biomarkers* (Vol. 7, Issue 4, pp. 269–290). <https://doi.org/10.1080/13547500210127318>
- Kerr, D., Grahame, G., & Nakouzi, G. (2012). Assays of pyruvate dehydrogenase complex and pyruvate carboxylase activity. *Methods in Molecular Biology*, 837, 93–119. [https://doi.org/10.1007/978-1-61779-504-6\\_7](https://doi.org/10.1007/978-1-61779-504-6_7)
- Ki, S. S., Jeong, J. M., Kim, S. H., et al. (2002). A case of neurotoxicity following 5-fluorouracil-based chemotherapy. *The Korean Journal of Internal Medicine*, 17(1), 73–77. <https://doi.org/10.3904/kjim.2002.17.1.73>
- Kim, J. H., Ahn, J. H., Barone, P. W., et al. (2010). A luciferase/single-walled carbon nanotube conjugate for nearInfrared fluorescent detection of cellular ATP. *Angewandte Chemie - International Edition*, 49(8), 1456–1459. <https://doi.org/10.1002/anie.200906251>
- Kitada, T., Asakawa, S., Hattori, N., et al. (1998). Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature*, 392(6676), 605–608. <https://doi.org/10.1038/33416>
- Kluckova, K., Sticha, M., Cerny, J., et al. (2015). Ubiquinone-binding site mutagenesis reveals the role of mitochondrial complex II in cell death initiation. *Cell Death and Disease*, 6(5). <https://doi.org/10.1038/cddis.2015.110>
- Kohonen, P., Parkkinen, J. A., Willighagen, E. L., et al. (2017). A transcriptomics data-driven gene space accurately predicts liver cytopathology and drug-induced liver injury. *Nature Communications*, 8. <https://doi.org/10.1038/ncomms15932>
- Kolde, R., (2019). pheatmap: Pretty Heatmaps. R package version 1.0.12. <https://CRAN.R-project.org/package=pheatmap>
- Koopman, W. J. H., Verkaar, S., Visch, H. J., et al. (2005). Inhibition of complex I of the electron transport chain causes O<sub>2</sub>-mediated mitochondrial outgrowth. *American Journal of Physiology - Cell Physiology*, 288(6), 1440–1450. <https://doi.org/10.1152/ajpcell.00607.2004>
- Koopman, W. J. H., Visch, H. J., Smeitink, J. A. M., et al. (2006). Simultaneous quantitative measurement and automated analysis of mitochondrial morphology, mass, potential, and motility in living human skin fibroblasts. *Cytometry Part A*, 69(1), 1–2. <https://doi.org/10.1002/cyto.a.20198>
- Korga, A., Ostrowska, M., Iwan, M., et al. (2019). Inhibition of glycolysis disrupts cellular antioxidant defense and sensitizes HepG2 cells to doxorubicin treatment. *FEBS Open Bio*, 9(5), 959–972. <https://doi.org/10.1002/2211-5463.12628>
- Kornick, K., Bogner, B., Sutter, L., et al. (2019). Population Dynamics of Mitochondria in Cells: A Minimal Mathematical Model. *Frontiers in Physics*, 7, 146. <https://doi.org/10.3389/fphy.2019.00146>
- Krall, A., Mullen, P., Surjono, F., et al. (2021). Asparagine couples mitochondrial respiration to ATF4 activity and tumor growth. *Cell Metabolism*, 33(5), 1013–1026.e6. <https://doi.org/10.1016/J.CMET.2021.02.001>
- Krebs, A., Nyffeler, J., Karreman, C., et al. (2020). Determination of benchmark concentrations and their statistical uncertainty for cytotoxicity test data and functional in vitro assays. *ALTEX*, 37(1), 155–163. <https://doi.org/10.14573/ALTEX.1912021>
- Krebs, A., Waldmann, T., Wilks, M., et al. (2019). Template for the description of cell-based toxicological test methods to allow evaluation and regulatory use of the data. *ALTEX*, 36(4), 682–699. <https://doi.org/10.14573/ALTEX.1909271>
- Krewski, D., Westphal, M., Andersen, M. E., et al. (2014). A framework for the next generation of risk science. In *Environmental Health Perspectives* (Vol. 122, Issue 8, pp. 796–805). <https://doi.org/10.1289/ehp.1307260>
- Krieger, R. I. (2001). Handbook of Pesticide Toxicology. In *Handbook of Pesticide Toxicology*. Elsevier. <https://doi.org/10.1016/b978-0-12-426260-7.x5000-9>
- Krug, A. K., Gutbier, S., Zhao, L., et al. (2014). Transcriptional and metabolic adaptation of human neurons to the mitochondrial toxicant MPP<sup>+</sup>. *Cell Death and Disease* 2014 5:5, 5(5), e1222–e1222. <https://doi.org/10.1038/cddis.2014.166>
- Kühl, I., Miranda, M., Atanassov, I., et al. (2017). Transcriptomic and proteomic landscape of mitochondrial dysfunction reveals secondary coenzyme Q deficiency in mammals. *eLife*, 6, e30952. <https://doi.org/10.7554/eLife.30952>
- Kuijper, I. A., Yang, H., Van De Water, B., et al. (2017). Unraveling cellular pathways contributing to drug-induced liver injury by dynamical modeling. In *Expert Opinion on Drug Metabolism and Toxicology* (Vol. 13, Issue 1, pp. 5–17). Taylor and Francis Ltd. <https://doi.org/10.1080/17425255.2017.1234607>

- Kunii, M., Doi, H., Higashiyama, Y., et al. (2015). A Japanese case of cerebellar ataxia, spastic paraparesis and deep sensory impairment associated with a novel homozygous TTC19 mutation. *Journal of Human Genetics*, 60(4), 187–191. <https://doi.org/10.1038/JHG.2015.7>
- Kwon, K. A., Kwon, H.-C., Kim, M. C., et al. (2010). A Case of 5-Fluorouracil Induced Encephalopathy. *Cancer Research and Treatment*, 42(2), 118–120. <https://doi.org/10.4143/crt.2010.42.2.118>
- Labib, S., Williams, A., Yauk, C. L., et al. (2016). Nano-risk Science: Application of toxicogenomics in an adverse outcome pathway framework for risk assessment of multi-walled carbon nanotubes. *Particle and Fibre Toxicology*, 13, 15. <https://doi.org/10.1186/s12989-016-0125-9>
- Lai, J. C. K., DiLorenzo, J. C., & Sheu, K. F. R. (1988). Pyruvate dehydrogenase complex is inhibited in calcium-loaded cerebrocortical mitochondria. *Neurochemical Research*, 13(11), 1043–1048. <https://doi.org/10.1007/BF00973148>
- Lareau, C. A., Ludwig, L. S., Muus, C., et al. (2020). Massively parallel single-cell mitochondrial DNA genotyping and chromatin profiling. *Nature Biotechnology*, 39(4), 451–461. <https://doi.org/10.1038/s41587-020-0645-6>
- Lee, D. H., Kim, S. Y., & Hong, J. I. (2004). A fluorescent pyrophosphate sensor with high selectivity over ATP in water. *Angewandte Chemie - International Edition*, 43(36), 4777–4780. <https://doi.org/10.1002/anie.200453914>
- Lee, E. H., Kim, S., Choi, M. S., et al. (2019). Gene networking in colistin-induced nephrotoxicity reveals an adverse outcome pathway triggered by proteotoxic stress. *International Journal of Molecular Medicine*, 43(3), 1343–1355. <https://doi.org/10.3892/ijmm.2019.4052>
- Lee, Y. C., Bååth, J. A., Bastle, R. M., et al. (2018). Impact of Detergents on Membrane Protein Complex Isolation. *Journal of Proteome Research*, 17(1), 348–358. <https://doi.org/10.1021/acs.jproteome.7b00599>
- Leist, M., Ghallab, A., Graepel, R., et al. (2017). Adverse outcome pathways: opportunities, limitations and open questions. *Archives of Toxicology*, 91(11), 3477–3505. <https://doi.org/10.1007/s00204-017-2045-3>
- Lemasters, J. J., & Ramshesh, V. K. (2007). Imaging of Mitochondrial Polarization and Depolarization with Cationic Fluorophores. In *Methods in Cell Biology* (Vol. 80, pp. 283–295). *Methods Cell Biol.* [https://doi.org/10.1016/S0091-679X\(06\)80014-2](https://doi.org/10.1016/S0091-679X(06)80014-2)
- Leonard, A. P., Cameron, R. B., Speiser, J. L., et al. (2015). Quantitative analysis of mitochondrial morphology and membrane potential in living cells using high-content imaging, machine learning, and morphological binning. *Biochim Biophys Acta*, 1853(2), 348–360. <https://doi.org/10.1016/j.bbamcr.2014.11.002>
- Li, H., Zhu, X., Yang, W., et al. (2014). Comparative kinetics of Qi site inhibitors of cytochrome bc1 complex: picomolar antimycin and micromolar cyazofamid. *Chemical Biology & Drug Design*, 83(1), 71–80. <https://doi.org/10.1111/CBDD.12199>
- Li, L., Wang, C., Yang, H., et al. (2017). Metabolomics reveal mitochondrial and fatty acid metabolism disorders that contribute to the development of DKD in T2DM patients. *Molecular BioSystems*, 13(11), 2392–2400. <https://doi.org/10.1039/c7mb00167c>
- Li, N., Ragheb, K., Lawler, G., et al. (2003). Mitochondrial complex I inhibitor rotenone induces apoptosis through enhancing mitochondrial reactive oxygen species production. *Journal of Biological Chemistry*, 278(10), 8516–8525. <https://doi.org/10.1074/jbc.M210432200>
- Li, Y., Li, X., Kan, Q., et al. (2017). Mitochondrial pyruvate carrier function is negatively linked to Warburg phenotype in vitro and malignant features in esophageal squamous cell carcinomas. *Oncotarget*, 8(1), 1058–1073. <https://doi.org/10.18632/oncotarget.13717>
- Liepinsh, E., Makrecka, M., Kuka, J., et al. (2014). Selective inhibition of OCTN2 is more effective than inhibition of gamma-butyrobetaine dioxygenase to decrease the availability of L-carnitine and to reduce myocardial infarct size. *Pharmacological Research*, 85, 33–38. <https://doi.org/10.1016/j.phrs.2014.05.002>
- Limonciel, A., Aschauer, L., Wilmes, A., et al. (2011). Lactate is an ideal non-invasive marker for evaluating temporal alterations in cell stress and toxicity in repeat dose testing regimes. *Toxicology in Vitro: An International Journal Published in Association with BIBRA*, 25(8), 1855–1862. <https://doi.org/10.1016/J.TIV.2011.05.018>
- Limonciel, A., G, A., G, C., et al. (2018). Comparison of base-line and chemical-induced transcriptomic responses in HepaRG and RPTC/TERT1 cells using TempO-Seq. *Archives of Toxicology*, 92(8), 2517–2531. <https://doi.org/10.1007/s00204-018-2256-2>
- Lindon, J. C., Keun, H. C., Ebbels, T. M. D., et al. (2005). The Consortium for Metabonomic Toxicology (COMET): Aims, activities and achievements. In *Pharmacogenomics* (Vol. 6, Issue 7, pp. 691–699). <https://doi.org/10.2217/14622416.6.7.691>
- Ling, N. (2003). Rotenone - A review of its toxicity and use for fisheries management. *Science for Conservation*.
- Liu, X., Xu, J., Lv, Y., et al. (2013). An ATP-selective, lanthanide complex luminescent probe. *Dalton Transactions*, 42(27), 9840–9846. <https://doi.org/10.1039/c3dt50986a>
- Liu, Y., Fiskum, G., & Schubert, D. (2002). Generation of reactive oxygen species by the mitochondrial electron transport chain. *Journal of Neurochemistry*, 80(5), 780–787. <https://doi.org/10.1046/j.0022-3042.2002.00744.x>
- Liu, Y., Jin, M., Wang, Y., et al. (2020). MCU-induced mitochondrial calcium uptake promotes mitochondrial biogenesis and colorectal cancer growth. *Signal Transduction and Targeted Therapy*, 5(1), 59. <https://doi.org/10.1038/s41392-020-0155-5>
- Liu, Y., Villamena, F. A., Sun, J., et al. (2009). Esterified trityl radicals as intracellular oxygen probes. *Free Radical Biology and Medicine*, 46(7), 876–883. <https://doi.org/10.1016/j.freeradbiomed.2008.12.011>
- Liu, Z., Yuan, J., Lasorella, A., et al. (2020). Integrating single-cell RNA-seq and imaging with SCOPE-seq2. *Scientific Reports*, 10(1), 1–15. <https://doi.org/10.1038/s41598-020-76599-w>
- Longo, D., Yang, Y., Watkins, P., et al. (2016). Elucidating Differences in the Hepatotoxic Potential of Tolcapone and Entacapone With DILIsym®, a Mechanistic Model of Drug-Induced Liver Injury. *CPT: Pharmacometrics & Systems Pharmacology*, 5(1), 31–39. <https://doi.org/10.1002/PSP4.12053>

- Longo, N., Amat Di San Filippo, C., & Pasquali, M. (2006). Disorders of carnitine transport and the carnitine cycle. *Am J Med Genet C - Semin Med Genet*, 142C(2), 77–85. <https://doi.org/10.1002/ajmg.c.30087>
- Los, F. C. O., Randis, T. M., Aroian, R. V., et al. (2013). Role of Pore-Forming Toxins in Bacterial Infectious Diseases. *Microbiol Mol Biol Rev*, 77(2), 173–207. <https://doi.org/10.1128/mmr.00052-12>
- Love, M. I., Huber, W., & Anders, S. (2014). Moderated estimation of fold change and dispersion for RNA-seq data with DESeq2. *Genome Biology*, 15(12), 550. <https://doi.org/10.1186/s13059-014-0550-8>
- Lowe, R., Shirley, N., Bleackley, M., et al. (2017). Transcriptomics technologies. *PLoS Computational Biology*, 13(5), e1005457. <https://doi.org/10.1371/journal.pcbi.1005457>
- Lümmen, P. (1998). Complex I inhibitors as insecticides and acaricides. *Biochim Biophys Acta*, 1364(2), 287–296. [https://doi.org/10.1016/S0005-2728\(98\)00034-6](https://doi.org/10.1016/S0005-2728(98)00034-6)
- Lynch, M., & Marinov, G. K. (2015). The bioenergetic costs of a gene. *Proceedings of the National Academy of Sciences of the United States of America*, 112(51), 15690–15695. <https://doi.org/10.1073/pnas.1514974112>
- Ma, Y., Wang, W., Devarakonda, T., et al. (2020). Functional analysis of molecular and pharmacological modulators of mitochondrial fatty acid oxidation. *Scientific Reports*, 10(1), 1450. <https://doi.org/10.1038/s41598-020-58334-7>
- MacVicar, T., & Langer, T. (2016). OPA1 processing in cell death and disease - the long and short of it. In *Journal of Cell Science* (Vol. 129, Issue 12, pp. 2297–2306). <https://doi.org/10.1242/jcs.159186>
- Maekawa, H., Inoue, T., Ouchi, H., et al. (2019). Mitochondrial Damage Causes Inflammation via cGAS-STING Signaling in Acute Kidney Injury. *Cell Reports*, 29(5), 1261–1273. <https://doi.org/10.1016/j.celrep.2019.09.050>
- Manfredi, G., Yang, L., Gajewski, C. D., et al. (2002). Measurements of ATP in mammalian cells. *Methods*, 26(4), 317–326. [https://doi.org/10.1016/S1046-2023\(02\)00037-3](https://doi.org/10.1016/S1046-2023(02)00037-3)
- Manzoni, C., Kia, D. A., Vandrovцова, J., et al. (2018). Genome, transcriptome and proteome: The rise of omics data and their integration in biomedical sciences. *Briefings in Bioinformatics*, 19(2), 286–302. <https://doi.org/10.1093/BIB/BBW114>
- Markova, S. V., Burakova, L. P., Golz, S., et al. (2012). The light-sensitive photoprotein berovim from the bioluminescent ctenophore *Beroë abyssicola*: A novel type of Ca<sup>2+</sup>-regulated photoprotein. *FEBS Journal*, 279(5), 856–870. <https://doi.org/10.1111/j.1742-4658.2012.08476.x>
- Markova, S. V., Vysotski, E. S., Blinks, J. R., et al. (2002). Obelin from the bioluminescent marine hydroid *Obelia geniculata*: Cloning, expression, and comparison of some properties with those of other Ca<sup>2+</sup>-regulated photoproteins. *Biochemistry*, 41(7), 2227–2236. <https://doi.org/10.1021/bi0117910>
- Marroquin, L. D., Hynes, J., Dykens, J. A., et al. (2007). Circumventing the crabtree effect: Replacing media glucose with galactose increases susceptibility of hepG2 cells to mitochondrial toxicants. *Toxicological Sciences*, 97(2), 539–547. <https://doi.org/10.1093/toxsci/kfm052>
- Martens, M., Ammar, A., Riutta, A., et al. (2021). WikiPathways: connecting communities. *Nucleic Acids Research*, 49(D1), D613–D621. <https://doi.org/10.1093/nar/gkaa1024>
- Martens, M., Verbruggen, T., Nymark, P., et al. (2018). Introducing WikiPathways as a Data-Source to Support Adverse Outcome Pathways for Regulatory Risk Assessment of Chemicals and Nanomaterials. *Frontiers in Genetics*, 9, 661. <https://doi.org/10.3389/fgene.2018.00661>
- Martin, W. F., Garg, S., & Zimorski, V. (2015). Endosymbiotic theories for eukaryote origin. In *Philos Trans R Soc B Biol Sci* (Vol. 370, Issue 1678, p. 20140330). <https://doi.org/10.1098/rstb.2014.0330>
- Massey, F. J. (1951). The Kolmogorov-Smirnov Test for Goodness of Fit. *Journal of the American Statistical Association*, 46(253), 68. <https://doi.org/10.2307/2280095>
- Mathon, C., Bovard, D., Dutertre, Q., et al. (2019). Impact of sample preparation upon intracellular metabolite measurements in 3D cell culture systems. *Metabolomics*, 15(6), 92. <https://doi.org/10.1007/s11306-019-1551-0>
- Mav, D., Shah, R. R., Howard, B. E., et al. (2018). A hybrid gene selection approach to create the S1500+ targeted gene sets for use in high-throughput transcriptomics. *PLoS ONE*, 13(2), e0191105. <https://doi.org/10.1371/journal.pone.0191105>
- McKenzie, M., Lim, S. C., & Duchon, M. R. (2017). Simultaneous measurement of mitochondrial calcium and mitochondrial membrane potential in live cells by fluorescent microscopy. *Journal of Visualized Experiments*, 2017(119), 55166. <https://doi.org/10.3791/55166>
- McKim, J. M., & Erickson, R. J. (1991). Environmental Impacts on the Physiological Mechanisms Controlling Xenobiotic Transfer across Fish Gills. *Physiological Zoology*, 64(1), 39–67. <https://doi.org/10.1086/physzool.64.1.30158513>
- McLafferty, F. W. (1980). Tandem Mass Spectrometry (MS/MS): A Promising New Analytical Technique for Specific Component Determination in Complex Mixtures. *Accounts of Chemical Research*, 13(2), 33–39. <https://doi.org/10.1021/ar50146a001>
- Meeusen, S. L., & Nunnari, J. (2017). Mitochondrial fusion in vitro. *Methods in Molecular Biology* (Clifton, N.J.), 372, 461–466. [https://doi.org/10.1007/978-1-59745-365-3\\_32](https://doi.org/10.1007/978-1-59745-365-3_32)
- Mehta, M. M., Weinberg, S. E., & Chandel, N. S. (2017). Mitochondrial control of immunity: Beyond ATP. In *Nature Reviews Immunology* (Vol. 17, Issue 10, pp. 608–620). <https://doi.org/10.1038/nri.2017.66>
- Melber, A., & Haynes, C. M. (2018). UPR mt regulation and output: A stress response mediated by mitochondrial-nuclear communication. In *Cell Research* (Vol. 28, Issue 3, pp. 281–295). <https://doi.org/10.1038/cr.2018.16>
- Memon, A. A., Zöller, B., Hedelius, A., et al. (2017). Quantification of mitochondrial DNA copy number in suspected cancer patients by a well optimized ddPCR method. *Biomolecular Detection and Quantification*, 13, 32–39. <https://doi.org/10.1016/j.bdq.2017.08.001>

- Mercer, T. R., Neph, S., Dinger, M. E., et al. (2011). The human mitochondrial transcriptome. *Cell*, 146(4), 645–658. <https://doi.org/10.1016/j.cell.2011.06.051>
- Merritt II, J. L., Norris, M., & Kanungo, S. (2018). Fatty acid oxidation disorders. *Annals of Translational Medicine*, 6(24), 473–473. <https://doi.org/10.21037/atm.2018.10.57>
- Merry, T. L., & Ristow, M. (2016). Mitohormesis in exercise training. *Free Radical Biology and Medicine*, 98, 123–130. <https://doi.org/10.1016/j.freeradbiomed.2015.11.032>
- Meyer, J. N., Hartman, J. H., & Mello, D. F. (2018). Mitochondrial Toxicity. *Toxicological Sciences*, 162(1), 15–23. <https://doi.org/10.1093/toxsci/kfy008>
- Meyer, J. N., Leung, M. C. K., Rooney, J. P., et al. (2013). Mitochondria as a target of environmental toxicants. In *Toxicological Sciences* (Vol. 134, Issue 1, pp. 1–17). <https://doi.org/10.1093/toxsci/kft102>
- Meyer, J. N., Leuthner, T. C., & Luz, A. L. (2017). Mitochondrial fusion, fission, and mitochondrial toxicity. *Toxicological Science*, 134(1), 1–17. <https://doi.org/10.1016/j.tox.2017.07.019>
- Microsoft Corporation, Weston, S. (2020). doParallel: Foreach Parallel Adaptor for the 'parallel' Package. R package version 1.0.16. <https://CRAN.R-project.org/package=doParallel>
- Mik, E. G., Johannes, T., Zuurber, C. J., et al. (2008). In vivo mitochondrial oxygen tension measured by a delayed fluorescence lifetime technique. *Biophysical Journal*, 95(8), 3977–3990. <https://doi.org/10.1529/biophysj.107.126094>
- Minta, A., Kao, J. P. Y., & Tsien, R. Y. (1989). Fluorescent indicators for cytosolic calcium based on rhodamine and fluorescein chromophores. *Journal of Biological Chemistry*, 264(14), 8171–8178. [https://doi.org/10.1016/s0021-9258\(18\)83165-9](https://doi.org/10.1016/s0021-9258(18)83165-9)
- Mishra, J., Davani, A. J., Natarajan, G. K., et al. (2019). Cyclosporin A Increases Mitochondrial Buffering of Calcium: An Additional Mechanism in Delaying Mitochondrial Permeability Transition Pore Opening. *Cells*, 8(9), 1052. <https://doi.org/10.3390/cells8091052>
- Miyawaki, A., Griesbeck, O., Heim, R., et al. (1999). Dynamic and quantitative Ca<sup>2+</sup> measurements using improved cameleons. *Proceedings of the National Academy of Sciences of the United States of America*, 96(5), 2135–2140. <https://doi.org/10.1073/pnas.96.5.2135>
- Miyawaki, A., Llopis, J., Heim, R., et al. (1997). Fluorescent indicators for Ca<sup>2+</sup> based on green fluorescent proteins and calmodulin. *Nature*, 388(6645), 882–887. <https://doi.org/10.1038/42264>
- Miyazono, Y., Hirashima, S., Ishihara, N., et al. (2018). Uncoupled mitochondria quickly shorten along their long axis to form indented spheroids, instead of rings, in a fission-independent manner. *Scientific Reports*, 8(1), 350. <https://doi.org/10.1038/s41598-017-18582-6>
- Monaghan, R. M., & Whitmarsh, A. J. (2015). Mitochondrial Proteins Moonlighting in the Nucleus. In *Trends in Biochemical Sciences* (Vol. 40, Issue 12, pp. 728–735). <https://doi.org/10.1016/j.tibs.2015.10.003>
- Morciano, G., Sarti, A. C., Marchi, S., et al. (2017). Use of luciferase probes to measure ATP in living cells and animals. *Nature Protocols*, 12(8), 1542–1562. <https://doi.org/10.1038/nprot.2017.052>
- Mordaunt, D., Jolley, A., Balasubramaniam, S., et al. (2015). Phenotypic variation of TTC19-deficient mitochondrial complex III deficiency: a case report and literature review. *American Journal of Medical Genetics. Part A*, 167(6), 1330–1336. <https://doi.org/10.1002/AJMG.A.36968>
- Moser, B. K. (1996). Maximum Likelihood Estimation and Related Topics. In *Linear Models Probability and Mathematical Statistics* (pp. 105–129). Elsevier. <https://doi.org/10.1016/b978-012508465-9/50006-5>
- Moshkforoush, A., Ashenagar, B., Tsoukias, N. M., et al. (2019). Modeling the role of endoplasmic reticulum-mitochondria microdomains in calcium dynamics. *Scientific Reports*, 9(1), 1–16. <https://doi.org/10.1038/s41598-019-53440-7>
- Münch, C. (2018). The different axes of the mammalian mitochondrial unfolded protein response. In *BMC Biology* (Vol. 16, Issue 1, p. 81). <https://doi.org/10.1186/s12915-018-0548-x>
- Murphey, W. H., Barnaby, C., Lin, F. J., et al. (1967). Malate dehydrogenases. II. Purification and properties of *Bacillus subtilis*, *Bacillus stearothermophilus*, and *Escherichia coli* malate dehydrogenases. *Journal of Biological Chemistry*, 242(7), 1548–1559. <https://pubmed.ncbi.nlm.nih.gov/4960671/>
- Murphy, S. M., Kieley, M., Jakeman, P. M., et al. (2016). Optimization of an in vitro bioassay to monitor growth and formation of myotubes in real time. *Bioscience Reports*, 36(3), e00330. <https://doi.org/10.1042/BSR20160036>
- Murrell, P. (2015). compare: Comparing Objects for Differences. R package version 0.2-6. <https://CRAN.R-project.org/package=compare>
- Muschet, C., Möller, G., Prehn, C., et al. (2016). Removing the bottlenecks of cell culture metabolomics: fast normalization procedure, correlation of metabolites to cell number, and impact of the cell harvesting method. *Metabolomics*, 12(10), 151. <https://doi.org/10.1007/s11306-016-1104-8>
- Mushtaq, M. Y., Choi, Y. H., Verpoorte, R., et al. (2014). Extraction for metabolomics: Access to the metabolome. In *Phytochemical Analysis* (Vol. 25, Issue 4, pp. 291–306). <https://doi.org/10.1002/pca.2505>
- Nadanaciva, S., Bernal, A., Aggeler, R., et al. (2007). Target identification of drug induced mitochondrial toxicity using immunocapture based OXPHOS activity assays. *Toxicology in Vitro*, 21(5), 902–911. <https://doi.org/10.1016/j.tiv.2007.01.011>
- Nadanaciva, S., Dykens, J., Bernal, A., et al. (2007). Mitochondrial impairment by PPAR agonists and statins identified via immunocaptured OXPHOS complex activities and respiration. *Toxicology and Applied Pharmacology*, 223(3), 277–287. <https://doi.org/10.1016/J.TAAP.2007.06.003>
- Nagai, T., Sawano, A., Eun Sun Park, et al. (2001). Circularly permuted green fluorescent proteins engineered to sense Ca<sup>2+</sup>. *Proc Natl Acad Sci USA*, 98(6), 3197–3202. <https://doi.org/10.1073/pnas.051636098>



- Nakai, J., Ohkura, M., & Imoto, K. (2001). A high signal-to-noise  $Ca^{2+}$  probe composed of a single green fluorescent protein. *Nature Biotechnology*, 19(2), 137–141. <https://doi.org/10.1038/84397>
- Nandipati, S., & Litvan, I. (2016a). Environmental exposures and Parkinson's disease. In *Int J Environ Res Public Health* (Vol. 13, Issue 9, p. 881). <https://doi.org/10.3390/ijerph13090881>
- Naven, R. T., Swiss, R., Klug-Mcleod, J., et al. (2013). The development of structure-activity relationships for mitochondrial dysfunction: Uncoupling of oxidative phosphorylation. *Toxicological Sciences*, 131(1), 271–278. <https://doi.org/10.1093/toxsci/kfs279>
- Nelson, D. L., & Cox, M. M. (2017). *Lehninger Principles of Biochemistry*. In W.H. Freeman and Company (Vol. 7).
- Neuwirth, E., (2014). RColorBrewer: ColorBrewer Palettes. R package version 1.1-2. <https://CRAN.R-project.org/package=RColorBrewer>
- Nicolson, G. L. (2014). Mitochondrial dysfunction and chronic disease: Treatment with natural supplements. *Integrative Medicine (Boulder)*, 13(4), 35–43. [/pmc/articles/PMC4566449/](https://pubmed.ncbi.nlm.nih.gov/24566449/)
- Nisoli, E., & Carruba, M. O. (2006). Nitric oxide and mitochondrial biogenesis. *Journal of Cell Science*, 119, 2855–2865. <https://doi.org/10.1242/jcs.03062>
- Nisoli, E., Clementi, E., Carruba, M. O., et al. (2007). Defective mitochondrial biogenesis: A hallmark of the high cardiovascular risk in the metabolic syndrome? In *Circulation Research* (Vol. 100, Issue 6, pp. 795–806). <https://doi.org/10.1161/01.RES.0000259591.97107.6c>
- Nisoli, E., Falcone, S., Tonello, C., et al. (2004). Mitochondrial biogenesis by NO yields functionally active mitochondria in mammals. *Proc Natl Acad Sci USA*, 101(47), 16507–16512. <https://doi.org/10.1073/pnas.0405432101>
- Nonnenmacher, Y., Palorini, R., d'Herouël, A. F., et al. (2017). Analysis of mitochondrial metabolism in situ: Combining stable isotope labeling with selective permeabilization. *Metabolic Engineering*, 43(Pt B), 147–155. <https://doi.org/10.1016/j.ymben.2016.12.005>
- Nymark, P., Rieswijk, L., Ehrhart, F., et al. (2018). A Data Fusion Pipeline for Generating and Enriching Adverse Outcome Pathway Descriptions. *Toxicological Sciences*, 62(1), 264–275. <https://doi.org/10.1093/toxsci/kfx252>
- OECD (1997), Test No. 424: Neurotoxicity Study in Rodents, OECD Guidelines for the Testing of Chemicals, Section 4, OECD Publishing, Paris, <https://doi.org/10.1787/9789264071025-en>
- OECD(2016).Guidance document for the use of adverse outcome pathways in developing integrated approaches to testing and assessment (IATA), Series on Testing & Assessment No.260, Paris, ENV/JM/MONO(2016)67[http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2016\)67&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2016)67&doclanguage=en)
- OECD (2019) Prediction of a 90 day repeated dose toxicity study (OECD 408) for 2-Ethylbutyric acid using a read-across approach from other branched carboxylic acids: Series on testing and assessment no. 324, ENV/JM/MONO(2020)20, <https://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm>
- OECD (2020a). van der Stel, W., Bennekou, S. H., Carta, G., Eakins, J., Delp, J., Forsby, A., Kamp, H., Gardner, I., Zdradil, B., Pastor, M., Gomes, J. C., White, A., Steger-Hartmann, T., Danen, E. H. J., Leist, M., Walker, P., Jennings, P., & van de Water, B. (2020). Case study on the use of integrated approaches to testing and assessment for identification and characterisation of parkinsonian hazard liability of deguelin by an aop-based testing and read across approach: Series on Testing and Assessment No. 326, ENV/JM/MONO(2020)22. <https://orbit.dtu.dk/en/publications/case-study-on-the-use-of-integrated-approaches-to-testing-and-ass-2>
- OECD (2020b). Bennekou, S. H., van der Stel, W., Carta, G., Eakins, J., Delp, J., Forsby, A., Kamp, H., Gardner, I., Zdradil, B., Pastor, M., Gomes, J. C., White, A., Steger-Hartmann, T., Danen, E. H. J., Leist, M., Walker, P., Jennings, P., & van de Water, B. (2020). Case study on the use of integrated approaches to testing and assessment for mitochondrial complex-iii-mediated neurotoxicity of azoxystrobin - read-across to other strobilurins: Series on testing and assessment no. 327, ENV/JM/MONO(2020)23 o <https://orbit.dtu.dk/en/publications/case-study-on-the-use-of-integrated-approaches-to-testing-and-ass>
- OECD (2020c), Report on considerations form case studies on integrated approaches for testing and assessment (IATA), Series on Testing & Assessment No.328, Paris, ENV/JM/MONO(2020)24 [http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono\(2020\)24&doclanguage=en](http://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=env/jm/mono(2020)24&doclanguage=en)
- Ockleford, C., Adriaanse, P., Beryn, P., et al. (2017). Investigation into experimental toxicological properties of plant protection products having a potential link to Parkinson's disease and childhood leukaemia. *EFSA Journal*. European Food Safety Authority, 15(3), e04691. <https://doi.org/10.2903/J.EFSA.2017.4691>
- Ohkura, M., Matsuzaki, M., Kasai, H., et al. (2005). Genetically encoded bright  $Ca^{2+}$  probe applicable for dynamic  $Ca^{2+}$  imaging of dendritic spines. *Analytical Chemistry*, 77(18), 5861–5869. <https://doi.org/10.1021/ac0506837>
- Ok, N. O., Farc, L., Abdelaziz, A., et al. (2019). Integrated analysis of in vitro data and the adverse outcome pathway framework for prioritization and regulatory applications: An exploratory case study using publicly available data on piperonyl butoxide and liver models. *Toxicology in Vitro*, 54, 23–32. <https://doi.org/10.1016/j.tiv.2018.09.002>
- Okun, J., Lümmen, P., & Brandt, U. (1999). Three classes of inhibitors share a common binding domain in mitochondrial complex I (NADH:ubiquinone oxidoreductase). *The Journal of Biological Chemistry*, 274(5), 2625–2630. <https://doi.org/10.1074/JBC.274.5.2625>
- Olszewska, A., & Szewczyk, A. (2013). Mitochondria as a pharmacological target: Magnum overview. In *IUBMB Life* (Vol. 65, Issue 3, pp. 273–281). <https://doi.org/10.1002/iub.1147>

- Ong, S. E., & Mann, M. (2007). A practical recipe for stable isotope labeling by amino acids in cell culture (SILAC). *Nature Protocols*, 1(6), 2650–2660. <https://doi.org/10.1038/nprot.2006.427>
- Oonthonpan, L., Rauckhorst, A. J., Gray, L. R., et al. (2019). Two human patient mitochondrial pyruvate carrier mutations reveal distinct molecular mechanisms of dysfunction. *JCI Insight*, 5(13), e126132. <https://doi.org/10.1172/jci.insight.126132>
- Ouellet, M., Guillebaud, G., Gervais, V., et al. (2017). A novel algorithm identifies stress-induced alterations in mitochondrial connectivity and inner membrane structure from confocal images. *PLoS Computational Biology*, 13(6), e1005612. <https://doi.org/10.1371/journal.pcbi.1005612>
- Owen, M. R., Doran, E., & Halestrap, A. P. (2000). Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. *Biochemical Journal*, 384(Pt 3), 607–614. <https://doi.org/10.1042/0264-6021:3480607>
- Özalp, V. C., Nielsen, L. J., & Olsen, L. F. (2010). An aptamer-based nanobiosensor for real-time measurements of ATP dynamics. *ChemBioChem*, 11(18), 2538–2541. <https://doi.org/10.1002/cbic.201000500>
- Pacheu-Grau, D., Rucktaeschel, R., & Deckers, M. (2018). Mitochondrial dysfunction and its role in tissue-specific cellular stress. *Cell Stress*, 2(8), 184–199. <https://doi.org/10.15698/cst2018.07.147>
- Padmanabhan, K., Eddy, W. F., & Crowley, J. C. (2010). A novel algorithm for optimal image thresholding of biological data. *Journal of Neuroscience Methods*, 193(2), 380–384. <https://doi.org/10.1016/j.jneumeth.2010.08.031>
- Pagès, H., Carlson, M., Falcon, S., Li, N. (2020). AnnotationDbi: Manipulation of SQLite-based annotations in Bioconductor. R package version 1.52.0, <https://bioconductor.org/packages/AnnotationDbi>
- Pagliarini, D. J., Calvo, S. E., Chang, B., et al. (2008). A Mitochondrial Protein Compendium Elucidates Complex I Disease Biology. *Cell*, 134(1), 112–123. <https://doi.org/10.1016/j.cell.2008.06.016>
- Palikaras, K., Lionaki, E., & Tavernarakis, N. (2018). Mechanisms of mitophagy in cellular homeostasis, physiology and pathology. In *Nature Cell Biology* (Vol. 20, Issue 9, pp. 1013–1022). <https://doi.org/10.1038/s41556-018-0176-2>
- Palmer, A. E., & Tsiens, R. Y. (2006). Measuring calcium signaling using genetically targetable fluorescent indicators. *Nature Protocols*, 1(3), 1057–1065. <https://doi.org/10.1038/nprot.2006.172>
- Pan, D., Lindau, C., Lagjes, S., et al. (2018). Metabolic profiling of isolated mitochondria and cytoplasm reveals compartment-specific metabolic responses. *Metabolomics*, 14(5), 59. <https://doi.org/10.1007/s11306-018-1352-x>
- Park, L. C. H., Calingasan, N. Y., Sheu, K. F. R., et al. (2000). Quantitative  $\alpha$ -ketoglutarate dehydrogenase activity staining in brain sections and in cultured cells. *Analytical Biochemistry*, 277(1), 86–93. <https://doi.org/10.1006/abio.1999.4359>
- Patergnani, S., & Pinton, P. (2015). Mitophagy and mitochondrial balance. *Methods in Molecular Biology* (Clifton, N.J.), 1241, 181–194. [https://doi.org/10.1007/978-1-4939-1875-1\\_15](https://doi.org/10.1007/978-1-4939-1875-1_15)
- Patten, D. A., Wong, J., Khacho, M., et al. (2014). OPA1-dependent cristae modulation is essential for cellular adaptation to metabolic demand. *The EMBO Journal*, 33(22), 2676–2691. <https://doi.org/10.15252/embj.201488349>
- Paupé, V., & Prudent, J. (2018). New insights into the role of mitochondrial calcium homeostasis in cell migration. *Biochem Biophys Res Commun*, 500(1), 75–86. <https://doi.org/10.1016/j.bbrc.2017.05.039>
- Pearson, B. L., Simon, J. M., McCoy, E. S., et al. (2016). Identification of chemicals that mimic transcriptional changes associated with autism, brain aging and neurodegeneration. *Nature Communications*, 7, 11173. <https://doi.org/10.1038/ncomms11173>
- Pearson, B., Simon, J., McCoy, E., et al. (2016). Identification of chemicals that mimic transcriptional changes associated with autism, brain aging and neurodegeneration. *Nature Communications*, 7, 11173. <https://doi.org/10.1038/NCOMMS11173>
- Peng, J. Y., Lin, C. C., Chen, Y. J., et al. (2011). Automatic morphological subtyping reveals new roles of caspases in mitochondrial dynamics. *PLoS Computational Biology*, 7(10), e1002212. <https://doi.org/10.1371/journal.pcbi.1002212>
- Penjweini, R., Andreoni, A., Rosales, T., et al. (2018). Intracellular oxygen mapping using a myoglobin-mCherry probe with fluorescence lifetime imaging. *Journal of Biomedical Optics*, 23(10), 1–14. <https://doi.org/10.1117/1.jbo.23.10.107001>
- Pereira, E. J., Smolko, C. M., & Janes, K. A. (2016). Computational models of reactive oxygen species as metabolic byproducts and signal-transduction modulators. In *Frontiers in Pharmacology* (Vol. 7, p. 457). *Frontiers Media S.A.* <https://doi.org/10.3389/fphar.2016.00457>
- Perry, S. W., Norman, J. P., Barbieri, J., et al. (2011). Mitochondrial membrane potential probes and the proton gradient: A practical usage guide. In *BioTechniques* (Vol. 50, Issue 2, pp. 98–115). *Biotechniques*. <https://doi.org/10.2144/000113610>
- Pessayre, D., Fromenty, B., Berson, A., et al. (2012). Central role of mitochondria in drug-induced liver injury. *Drug Metabolism Reviews*, 44(1), 34–87. <https://doi.org/10.3109/03602532.2011.604086>
- Peter, B., Waddington, C. L., Oláhová, M., et al. (2018). Defective mitochondrial protease LonP1 can cause classical mitochondrial disease. *Human Molecular Genetics*, 27(10), 1743–1753. <https://doi.org/10.1093/hmg/ddy080>
- Pfanner, N., Warscheid, B., & Wiedemann, N. (2019). Mitochondrial proteins: from biogenesis to functional networks. In *Nature Reviews Molecular Cell Biology* (Vol. 20, Issue 5, pp. 267–284). <https://doi.org/10.1038/s41580-018-0092-0>
- Pfleger, J., He, M., & Abdellatif, M. (2015). Mitochondrial complex II is a source of the reserve respiratory capacity that is regulated by metabolic sensors and promotes cell survival. *Cell Death & Disease*, 6(7). <https://doi.org/10.1038/CDDIS.2015.202>
- Phillips, J. R., Svoboda, D. L., Tandon, A., et al. (2019). BMD Express 2: Enhanced transcriptomic dose-response analysis workflow. *Bioinformatics*, 35(10), 1780–1782. <https://doi.org/10.1093/bioinformatics/bty878>
- Phillips, M. J., & Voeltz, G. K. (2016). Structure and function of ER membrane contact sites with other organelles. In *Nature Reviews Molecular Cell Biology* (Vol. 17, Issue 2, pp. 69–82). <https://doi.org/10.1038/nrm.2015.8>

- Pietzke, M., Zasada, C., Mudrich, S., et al. (2014). Decoding the dynamics of cellular metabolism and the action of 3-bromopyruvate and 2-deoxyglucose using pulsed stable isotope-resolved metabolomics. *Cancer & Metabolism*, 2, 9. <https://doi.org/10.1186/2049-3002-2-9>
- Pirzada, N. A., Ali, I. I., & Dafer, R. M. (2000). Fluorouracil-induced neurotoxicity. *Annals of Pharmacotherapy*, 34(1), 35–38. <https://doi.org/10.1345/aph.18425>
- Popov, L.-D., & Simionescu, N. (2020). Mitochondrial biogenesis: An update. *J Cell Mol Med*, 24(9), 4892–4899. <https://doi.org/10.1111/jcmm.15194>
- Porceddu, M., Buron, N., Roussel, C., et al. (2012). Prediction of liver injury induced by chemicals in human with a multiparametric assay on isolated mouse liver mitochondria. *Toxicological Sciences*, 129(2), 332–345. <https://doi.org/10.1093/toxsci/kfs197>
- Porter, R. K., & Brand, M. D. (1995). Mitochondrial proton conductance and H<sup>+</sup>/O ratio are independent of electron transport rate in isolated hepatocytes. *Biochemical Journal*, 310(2), 379–382. <https://doi.org/10.1042/bj3100379>
- Poser, I., Sarov, M., Hutchins, J. R. A., et al. (2008). BAC TransgeneOmics: A high-throughput method for exploration of protein function in mammals. *Nature Methods*, 5(5), 405–415. <https://doi.org/10.1038/nmeth.1199>
- Poulin, P., & Theil, F. (2002). Prediction of pharmacokinetics prior to in vivo studies. 1. Mechanism-based prediction of volume of distribution. *Journal of Pharmaceutical Sciences*, 91(1), 129–156. <https://doi.org/10.1002/JPS.10005>
- Prudent, J., & McBride, H. M. (2017). The mitochondria–endoplasmic reticulum contact sites: a signalling platform for cell death. In *Current Opinion in Cell Biology* (Vol. 47, pp. 52–63). <https://doi.org/10.1016/j.ceb.2017.03.007>
- Puigvert, J. C., Von Stechow, L., Siddappa, R., et al. (2013). Systems biology approach identifies the kinase Csnk1a1 as a regulator of the DNA damage response in embryonic stem cells. *Science Signaling*, 6(259), ra5. <https://doi.org/10.1126/scisignal.2003208>
- Puschmann, A., Fiesel, F. C., Caulfield, T. R., et al. (2017). Heterozygous PINK1 p.G411S increases risk of Parkinson's disease via a dominant-negative mechanism. *Brain*, 140(1), 98–117. <https://doi.org/10.1093/brain/aww261>
- Qin, C., Yang, G., Yang, J., et al. (2020). Metabolism of pancreatic cancer: Paving the way to better anticancer strategies. In *Molecular Cancer* (Vol. 19, Issue 1, p. 50). BioMed Central Ltd. <https://doi.org/10.1186/s12943-020-01169-7>
- Quirós, P. M., Mottis, A., & Auwerx, J. (2016). Mitonuclear communication in homeostasis and stress. In *Nature Reviews Molecular Cell Biology* (Vol. 17, Issue 4, pp. 213–226). Nature Publishing Group. <https://doi.org/10.1038/nrm.2016.23>
- Qureshi, M. A., Haynes, C. M., & Pellegrino, M. W. (2017). The mitochondrial unfolded protein response: Signaling from the powerhouse. In *Journal of Biological Chemistry* (Vol. 292, Issue 33, pp. 13500–13506). <https://doi.org/10.1074/jbc.R117.791061>
- Rabilloud, T., & Lescuyer, P. (2015). Proteomics in mechanistic toxicology: History, concepts, achievements, caveats, and potential. In *Proteomics* (Vol. 15, Issues 5–6, pp. 1051–1074). <https://doi.org/10.1002/pmic.201400288>
- Rajendran, M., Dane, E., Conley, J., et al. (2016). Imaging adenosine triphosphate (ATP). In *Biological Bulletin* (Vol. 231, Issue 1, pp. 73–84). Marine Biological Laboratory. <https://doi.org/10.1086/689592>
- Ramaiahgari, S., den Braver, M., Herpers, B., et al. (2014). A 3D in vitro model of differentiated HepG2 cell spheroids with improved liver-like properties for repeated dose high-throughput toxicity studies. *Archives of Toxicology*, 88(5), 1083–1095. <https://doi.org/10.1007/S00204-014-1215-9>
- Rana, P., Aleo, M. D., Gosink, M., et al. (2019). Evaluation of in Vitro Mitochondrial Toxicity Assays and Physicochemical Properties for Prediction of Organ Toxicity Using 228 Pharmaceutical Drugs. In *Chemical Research in Toxicology* (Vol. 32, Issue 1, pp. 156–167). <https://doi.org/10.1021/acs.chemrestox.8b00246>
- Rao, V. K., Carlson, E. A., & Yan, S. S. (2014). Mitochondrial permeability transition pore is a potential drug target for neurodegeneration. In *Biochimica et Biophysica Acta - Molecular Basis of Disease* (Vol. 1842, Issue 8, pp. 1267–1272). <https://doi.org/10.1016/j.bbadis.2013.09.003>
- Rasola, A., & Bernardi, P. (2011). Mitochondrial permeability transition in Ca<sup>2+</sup>-dependent apoptosis and necrosis. In *Cell Calcium* (Vol. 50, Issue 3, pp. 222–233). <https://doi.org/10.1016/j.ceca.2011.04.007>
- Ratti, M., Lampis, A., Ghidini, M., et al. (2020). MicroRNAs (miRNAs) and Long Non-Coding RNAs (lncRNAs) as New Tools for Cancer Therapy: First Steps from Bench to Bedside. In *Targeted Oncology* (Vol. 15, Issue 3, pp. 261–278). <https://doi.org/10.1007/s11523-020-00717-x>
- Raue, A., Kreutz, C., Maiwald, T., et al. (2009). Structural and practical identifiability analysis of partially observed dynamical models by exploiting the profile likelihood. *Bioinformatics*, 25(15), 1923–1929. <https://doi.org/10.1093/bioinformatics/btp358>
- Raue, A., Schilling, M., Bachmann, J., et al. (2013). Lessons Learned from Quantitative Dynamical Modeling in Systems Biology. *PLoS ONE*, 8(9), e74335. <https://doi.org/10.1371/journal.pone.0074335>
- Rauthan, M., & Pilon, M. (2015). A chemical screen to identify inducers of the mitochondrial unfolded protein response in *C. elegans*. *Worm*, 4(4), e1096490. <https://doi.org/10.1080/21624054.2015.1096490>
- Reddy, P. H. (2014). Increased mitochondrial fission and neuronal dysfunction in Huntington's disease: Implications for molecular inhibitors of excessive mitochondrial fission. In *Drug Discovery Today* (Vol. 19, Issue 7, pp. 951–955). <https://doi.org/10.1016/j.drudis.2014.03.020>
- Reisch, A. S., & Elpeleg, O. (2007). Biochemical Assays for Mitochondrial Activity: Assays of TCA Cycle Enzymes and PDHc. In *Methods in Cell Biology* (Vol. 80, pp. 199–222). *Methods Cell Biol.* [https://doi.org/10.1016/S0091-679X\(06\)80010-5](https://doi.org/10.1016/S0091-679X(06)80010-5)
- Reynolds, D. (2009). Gaussian Mixture Models. In *Encyclopedia of Biometrics* (pp. 659–663). Springer US. [https://doi.org/10.1007/978-0-387-73003-5\\_196](https://doi.org/10.1007/978-0-387-73003-5_196)

- Ribeiro, S. M., Giménez-Cassina, A., & Danial, N. N. (2015). Measurement of mitochondrial oxygen consumption rates in mouse primary neurons and astrocytes. *Methods in Molecular Biology*, 1241, 59–69. [https://doi.org/10.1007/978-1-4939-1875-1\\_6](https://doi.org/10.1007/978-1-4939-1875-1_6)
- Ritchie, M. E., Phipson, B., Wu, D., et al. (2015). Limma powers differential expression analyses for RNA-sequencing and microarray studies. *Nucleic Acids Research*, 43(7), e47. <https://doi.org/10.1093/nar/gkv007>
- Rizzuto, R., Simpson, A. W. M., Brini, M., et al. (1992). Rapid changes of mitochondrial  $\text{Ca}^{2+}$  revealed by specifically targeted recombinant aequorin. *Nature*, 358(6384), 325–327. <https://doi.org/10.1038/358325a0>
- Rodgers, T., & Rowland, M. (2006). Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. *Journal of Pharmaceutical Sciences*, 95(6), 1238–1257. <https://doi.org/10.1002/JPS.20502>
- Rodrigues, R. M., Kollipara, L., Chaudhari, U., et al. (2018). Omics-based responses induced by bosentan in human hepatoma HepaRG cell cultures. *Archives of Toxicology*, 92(6), 1939–1952. <https://doi.org/10.1007/s00204-018-2214-z>
- Rodríguez-Enríquez, S., Juárez, O., Rodríguez-Zavala, J. S., et al. (2001). Multisite control of the Crabtree effect in ascites hepatoma cells. *European Journal of Biochemistry*, 268(8), 2512–2519. <https://doi.org/10.1046/j.1432-1327.2001.02140.x>
- Rodríguez-Martín, T., Pooler, A. M., Lau, D. H. W., et al. (2016). Reduced number of axonal mitochondria and tau hypophosphorylation in mouse P301L tau knockin neurons. *Neurobiology of Disease*, 85, 1–10. <https://doi.org/10.1016/j.nbd.2015.10.007>
- Ron, D., & Walter, P. (2007). Signal integration in the endoplasmic reticulum unfolded protein response. In *Nature Reviews Molecular Cell Biology* (Vol. 8, Issue 7, pp. 519–529). <https://doi.org/10.1038/nrm2199>
- Rosenberger, C., Rosen, S., Paliege, A., et al. (2009). Pimonidazole adduct immunohistochemistry in the rat kidney: Detection of tissue hypoxia. *Methods in Molecular Biology*, 466, 161–174. [https://doi.org/10.1007/978-1-59745-352-3\\_12](https://doi.org/10.1007/978-1-59745-352-3_12)
- Ross, M. F., Da Ros, T., Blaikie, F. H., et al. (2006). Accumulation of lipophilic dications by mitochondria and cells. *Biochemical Journal*, 400(1), 199–208. <https://doi.org/10.1042/BJ20060919>
- Rowland, A. A., & Voeltz, G. K. (2012). Endoplasmic reticulum-mitochondria contacts: Function of the junction. In *Nature Reviews Molecular Cell Biology* (Vol. 13, Issue 10, pp. 607–625). <https://doi.org/10.1038/nrm3440>
- RStudio Team. (2016). RStudio: Integrated Development for R. 2016.
- Rudis, B., Bolker, B., Schulz, J., (2017). ggalt: Extra Coordinate Systems, 'Geoms', Statistical Transformations, Scales and Fonts for 'ggplot2'. R package version 0.4.0. <https://CRAN.R-project.org/package=ggalt>
- Rumsey, W. L., Vanderkooi, J. M., & Wilson, D. F. (1988). Imaging of phosphorescence: A novel method for measuring oxygen distribution in perfused tissue. *Science*, 241(4873), 1649–1651. <https://doi.org/10.1126/science.3420417>
- Ruprecht, J., Yankovskaya, V., Maklashina, E., et al. (2009). Structure of Escherichia coli succinate:quinone oxidoreductase with an occupied and empty quinone-binding site. *The Journal of Biological Chemistry*, 284(43), 29836–29846. <https://doi.org/10.1074/JBC.M109.010058>
- Rustin, P., Bourgeron, T., Parfait, B., et al. (1997). Inborn errors of the Krebs cycle: A group of unusual mitochondrial diseases in human. *Biochim Biophys Acta*, 1361(2), 185–197. [https://doi.org/10.1016/S0925-4439\(97\)00035-5](https://doi.org/10.1016/S0925-4439(97)00035-5)
- Sabbaha, H. N., & Stanley, W. C. (2002). Partial fatty acid oxidation inhibitors: A potentially new class of drugs for heart failure. In *European Journal of Heart Failure* (Vol. 4, Issue 1, pp. 3–6). [https://doi.org/10.1016/S1388-9842\(01\)00183-0](https://doi.org/10.1016/S1388-9842(01)00183-0)
- Sacks, W., Esser, A. H., & Sacks, S. (1991). Inhibition of pyruvate dehydrogenase complex (PDHC) by antipsychotic drugs. *Biological Psychiatry*, 29(2), 176–182. [https://doi.org/10.1016/0006-3223\(91\)90046-O](https://doi.org/10.1016/0006-3223(91)90046-O)
- Salabei, J., Gibb, A., & Hill, B. (2014). Comprehensive measurement of respiratory activity in permeabilized cells using extracellular flux analysis. *Nature Protocols*, 9(2), 421–438. <https://doi.org/10.1038/NPROT.2014.018>
- Samanta, K., Mirams, G. R., & Parekh, A. B. (2018). Sequential forward and reverse transport of the  $\text{Na}^+$   $\text{Ca}^{2+}$  exchanger generates  $\text{Ca}^{2+}$  oscillations within mitochondria. *Nature Communications*, 9(1), 156. <https://doi.org/10.1038/s41467-017-02638-2>
- Sandoval-Acuña, C., Lopez-Alarcón, C., Aliaga, M. E., et al. (2012). Inhibition of mitochondrial complex i by various non-steroidal anti-inflammatory drugs and its protection by quercetin via a coenzyme Q-like action. *Chemico-Biological Interactions*, 199(1), 18–28. <https://doi.org/10.1016/j.cbi.2012.05.006>
- Sangar, M. C., Bansal, S., & Avadhani, N. G. (2010). Bimodal targeting of microsomal cytochrome P450s to mitochondria: Implications in drug metabolism and toxicity. In *Expert Opinion on Drug Metabolism and Toxicology* (Vol. 6, Issue 10, pp. 1231–1251). <https://doi.org/10.1517/17425255.2010.503955>
- SAPEA, Science Advice for Policy by European Academies. (2018) Improving authorisation processes for plant protection products in Europe: a scientific perspective on the potential risks to human health. Berlin: SAPEA. <https://doi.org/10.26356/plantprotectionproducts>
- Sarewicz, M., & Osyczka, A. (2015). Electronic connection between the quinone and cytochrome C redox pools and its role in regulation of mitochondrial electron transport and redox signaling. *Physiological Reviews*, 95(1), 219–243. <https://doi.org/10.1152/PHYSREV.00006.2014>
- Sargsyan, A., Cai, J., Fandino, L. B., et al. (2015). Rapid parallel measurements of macroautophagy and mitophagy in mammalian cells using a single fluorescent biosensor. *Scientific Reports*, 5, 12397. <https://doi.org/10.1038/srep12397>
- Satoh, T., Miyoshi, H., Sakamoto, K., et al. (1996). Comparison of the inhibitory action of synthetic capsaicin analogues with various NADH-ubiquinone oxidoreductases. *Biochimica et Biophysica Acta*, 1273(1), 21–30. [https://doi.org/10.1016/0005-2728\(95\)00131-X](https://doi.org/10.1016/0005-2728(95)00131-X)

- Schell, J. C., Olson, K. A., Jiang, L., et al. (2014). A role for the mitochondrial pyruvate carrier as a repressor of the warburg effect and colon cancer cell growth. *Molecular Cell*, 56(3), 400–413. <https://doi.org/10.1016/j.molcel.2014.09.026>
- Schmidt, A., Kellermann, J., & Lottspeich, F. (2005). A novel strategy for quantitative proteomics using isotope-coded protein labels. *Proteomics*, 5(1), 4–15. <https://doi.org/10.1002/pmic.200400873>
- Schreyer, A., & T. B. (2012). USRCAT: real-time ultrafast shape recognition with pharmacophoric constraints. *Journal of Cheminformatics*, 4(1), 27. <https://doi.org/10.1186/1758-2946-4-27>
- Schuler, F., Yano, T., S. D. B., et al. (1999). NADH-quinone oxidoreductase: PSST subunit couples electron transfer from iron-sulfur cluster N2 to quinone. *Proceedings of the National Academy of Sciences of the United States of America*, 96(7), 4149–4153. <https://doi.org/10.1073/PNAS.96.7.4149>
- Schwab, M. A., Kölker, S., Van Den Heuvel, L. P., et al. (2005). Optimized spectrophotometric assay for the completely activated pyruvate dehydrogenase complex in fibroblasts. *Clinical Chemistry*, 51(1), 151–160. <https://doi.org/10.1373/clinchem.2004.033852>
- Seabold, S., & Perktold, J. (2010). *Statsmodels: Econometric and Statistical Modeling with Python*. Proceedings of the 9th Python in Science Conference. <https://doi.org/10.25080/majora-92bf1922-011>
- Seo, A. Y., Joseph, A. M., Dutta, D., et al. (2010). New insights into the role of mitochondria in aging: Mitochondrial dynamics and more. In *Journal of Cell Science* (Vol. 123, Issue Pt 15, pp. 2533–2542). <https://doi.org/10.1242/jcs.070490>
- Serra, A., Fratello, M., Cattelani, L., et al. (2020). Transcriptomics in Toxicogenomics, Part III: Data Modelling for Risk Assessment. In *Nanomaterials* (Vol. 4, pp. 708–710). <https://doi.org/10.3390/nano10040708>
- Shah, I., Woodrow Setzer, R., Jack, J., et al. (2016). Using toxcast™ data to reconstruct dynamic cell state trajectories and estimate toxicological points of departure. *Environmental Health Perspectives*, 124(7), 910–919. <https://doi.org/10.1289/ehp.1409029>
- Shan, J., Lopez, M. C., Baker, H. V., et al. (2010). Expression profiling after activation of amino acid deprivation response in HepG2 human hepatoma cells. *Physiological Genomics*, 41(3), 315–327. <https://doi.org/10.1152/physiolgenomics.00217.2009>
- Sharma, L., Lu, J., & Bai, Y. (2009). Mitochondrial respiratory complex I: structure, function and implication in human diseases. *Current Medicinal Chemistry*, 16(10), 1266–1277. <https://doi.org/10.2174/092986709787846578>
- Shebley, M., Sandhu, P., Emami Riedmaier, A., et al. (2018). Physiologically Based Pharmacokinetic Model Qualification and Reporting Procedures for Regulatory Submissions: A Consortium Perspective. *Clinical Pharmacology & Therapeutics*, 104(1), 88–110. <https://doi.org/10.1002/cpt.1013>
- Shi, Y., Inoue, H., Wu, J. C., et al. (2017). Induced pluripotent stem cell technology: A decade of progress. In *Nature Reviews Drug Discovery* (Vol. 16, Issue 2, pp. 115–130). Nature Publishing Group. <https://doi.org/10.1038/nrd.2016.245>
- Shiio, Y., & Aebersold, R. (2006). Quantitative proteome analysis using isotope-coded affinity tags and mass spectrometry. *Nature Protocols*, 1(1), 139–145. <https://doi.org/10.1038/nprot.2006.22>
- Shoshan-Barmatz, V., & Mizrahi, D. (2012). VDAC1: from structure to cancer therapy. *Frontiers in Oncology*, 29(2), 164. <https://doi.org/10.3389/fonc.2012.00164>
- Shpilka, T., & Haynes, C. M. (2018). The mitochondrial UPR: Mechanisms, physiological functions and implications in ageing. In *Nature Reviews Molecular Cell Biology* (Vol. 19, Issue 2, pp. 109–120). <https://doi.org/10.1038/nrm.2017.110>
- Sierotzki, H., & Scalliet, G. (2013). A review of current knowledge of resistance aspects for the next-generation succinate dehydrogenase inhibitor fungicides. *Phytopathology*, 103(9), 880–887. <https://doi.org/10.1094/PHYTO-01-13-0009-RVW>
- Sies, H., Berndt, C., & Jones, D. P. (2017). Oxidative Stress: Annual Review of Biochemistry. *Annual Review of Biochemistry*, 86, 715–748. <https://doi.org/10.1146/annurev-biochem-061516-045037>
- Simon, J. M., Paranjape, S. R., Wolter, J. M., et al. (2019). High-throughput screening and classification of chemicals and their effects on neuronal gene expression using RASL-seq. *Scientific Reports*, 9(1), 4529. <https://doi.org/10.1038/s41598-019-39016-5>
- Smirnova, E., Griparic, L., Shurland, D. L., et al. (2001). Dynammin-related protein Drp1 is required for mitochondrial division in mammalian cells. *Molecular Biology of the Cell*, 12(8), 2245–2256. <https://doi.org/10.1091/mbc.12.8.2245>
- Smith, A. C., Eyassou, F., Mazat, J. P., et al. (2017). MitoCore: A curated constraint-based model for simulating human central metabolism. *BMC Systems Biology*, 11(1), 114. <https://doi.org/10.1186/s12918-017-0500-7>
- Smith, L. C., Lavelle, C. M., Silva-Sanchez, C., et al. (2018). Early phosphoproteomic changes for adverse outcome pathway development in the fathead minnow (*Pimephales promelas*) brain. *Scientific Reports*, 8(1), 10212. <https://doi.org/10.1038/s41598-018-28395-w>
- Smith, L., Villaret-Cazadamont, J., Claus, S. P., et al. (2020). Important considerations for sample collection in metabolomics studies with a special focus on applications to liver functions. In *Metabolites* (Vol. 10, Issue 3, p. 104). <https://doi.org/10.3390/metabo10030104>
- Sommer, C., Straehle, C., Kothe, U., et al. (2011). Ilastik: Interactive learning and segmentation toolkit. *Proceedings - International Symposium on Biomedical Imaging*, 230–233. <https://doi.org/10.1109/ISBI.2011.5872394>
- Spagou, K., Wilson, I. D., Masson, P., et al. (2011). HILIC-UPLC-MS for exploratory urinary metabolic profiling in toxicological studies. *Analytical Chemistry*, 83(1), 382–390. <https://doi.org/10.1021/ac102523q>
- Späth, M. R., Bartram, M. P., Palacio-Escat, N., et al. (2019). The proteome microenvironment determines the protective effect of preconditioning in cisplatin-induced acute kidney injury. *Kidney International*, 95(2), 333–349. <https://doi.org/10.1016/j.kint.2018.08.037>

- Speidel, D. (2015). The role of DNA damage responses in p53 biology. In *Archives of Toxicology* (Vol. 89, Issue 4, pp. 501–517). <https://doi.org/10.1007/s00204-015-1459-z>
- Stelzer, G., Rosen, N., Plaschkes, I., et al. (2016). The GeneCards suite: From gene data mining to disease genome sequence analyses. *Current Protocols in Bioinformatics*, 54, 1.30.1-1.30.33. <https://doi.org/10.1002/cpbi.5>
- Stowe, D. F., & Camara, A. K. S. (2009). Mitochondrial reactive oxygen species production in excitable cells: Modulators of mitochondrial and cell function. In *Antioxidants and Redox Signaling* (Vol. 11, Issue 6, pp. 1373–1414). *Antioxid Redox Signal*. <https://doi.org/10.1089/ars.2008.2331>
- Strauss, K. A., Jinks, R. N., Puffenberger, E. G., et al. (2015). CODAS syndrome is associated with mutations of LONP1, encoding mitochondrial AAA+ Ion protease. *American Journal of Human Genetics*, 96(1), 121–135. <https://doi.org/10.1016/j.ajhg.2014.12.003>
- Suárez-Rivero, J., Villanueva-Paz, M., de la Cruz-Ojeda, P., et al. (2016). Mitochondrial Dynamics in Mitochondrial Diseases. *Diseases*, 5(1), 1. <https://doi.org/10.3390/diseases5010001>
- Sutherland, J. J., Webster, Y. W., Willy, J. A., et al. (2018). Toxicogenomic module associations with pathogenesis: A network-based approach to understanding drug toxicity. *Pharmacogenomics Journal*, 18(3), 377–390. <https://doi.org/10.1038/tpj.2017.17>
- Symersky, J., Osowski, D., Walters, D. E., et al. (2012a). Oligomycin frames a common drug-binding site in the ATP synthase. *Proc Natl Acad Sci USA*, 109(35), 13961–13965. <https://doi.org/10.1073/pnas.1207912109>
- Symersky, J., Osowski, D., Walters, D. E., et al. (2012b). Oligomycin frames a common drug-binding site in the ATP synthase. *Proc Natl Acad Sci USA*, 109(35), 13961–13965. <https://doi.org/10.1073/pnas.1207912109>
- Takahashi, E., Takano, T., Nomura, Y., et al. (2006). In vivo oxygen imaging using green fluorescent protein. *American Journal of Physiology - Cell Physiology*, 291(4), C781–C787. <https://doi.org/10.1152/ajpcell.00067.2006>
- Tanner, C., Kamel, F., Ross, G., et al. (2011). Rotenone, paraquat, and Parkinson's disease. *Environmental Health Perspectives*, 119(6), 866–872. <https://doi.org/10.1289/EHP.1002839>
- Tanner, C. M., Ross, G. W., Jewell, S. A., et al. (2009). Occupation and risk of parkinsonism: A multicenter case-control study. *Archives of Neurology*, 66(9), 1106–1113. <https://doi.org/10.1001/archneuro.2009.195>
- Tarca, A. L., Carey, V. J., Chen, X. wen, et al. (2007). Machine learning and its applications to biology. In *PLoS computational biology* (Vol. 3, Issue 6, p. e116). <https://doi.org/10.1371/journal.pcbi.0030116>
- Terron, A., Bal-Price, A., Paini, A., et al. (2018). An adverse outcome pathway for parkinsonian motor deficits associated with mitochondrial complex I inhibition. *Archives of Toxicology*, 92(1), 41–82. <https://doi.org/10.1007/S00204-017-2133-4>
- Thomas, B., & Flint Beal, M. (2007). Parkinson's disease. In *Human Molecular Genetics* (Vol. 16, Issue Spec No. 2, pp. R183–R194). <https://doi.org/10.1093/hmg/ddm159>
- Tian, Q., Stepaniants, S. B., Mao, M., et al. (2004). Integrated genomic and proteomic analyses of gene expression in mammalian cells. *Molecular and Cellular Proteomics*, 3(10), 960–969. <https://doi.org/10.1074/mcp.M400055-MCP200>
- Tian, Y., Li, B., Shi, W. Z., et al. (2014). Dynamin-related protein 1 inhibitors protect against ischemic toxicity through attenuating mitochondrial  $Ca^{2+}$  uptake from endoplasmic reticulum store in PC12 cells. *International Journal of Molecular Sciences*, 15(2), 3172–3185. <https://doi.org/10.3390/ijms15023172>
- Tilmant, K., Gerets, H., De Ron, P., et al. (2018). In vitro screening of cell bioenergetics to assess mitochondrial dysfunction in drug development. *Toxicology in Vitro: An International Journal Published in Association with BIBRA*, 52, 374–383. <https://doi.org/10.1016/J.TIV.2018.07.012>
- Titz, B., Elamin, A., Martin, F., et al. (2014). Proteomics for systems toxicology. In *Computational and Structural Biotechnology Journal* (Vol. 11, Issue 18, pp. 73–90). <https://doi.org/10.1016/j.csbj.2014.08.004>
- To, T. L., Cuadros, A. M., Shah, H., et al. (2019). A Compendium of Genetic Modifiers of Mitochondrial Dysfunction Reveals Intra-organelle Buffering. *Cell*, 179(5), 1222-1238.e17. <https://doi.org/10.1016/j.cell.2019.10.032>
- Tocilescu, M., Zickermann, V., Zwicker, K., et al. (2010). Quinone binding and reduction by respiratory complex I. *Biochimica et Biophysica Acta*, 1797(12), 1883–1890. <https://doi.org/10.1016/J.BBABIO.2010.05.009>
- Troger, F., Delp, J., Funke, M., et al. (2020). Identification of mitochondrial toxicants by combined in silico and in vitro studies – A structure-based view on the adverse outcome pathway. *Computational Toxicology*, 14, 100123. <https://doi.org/10.1016/J.COMTOX.2020.100123>
- Tulli, S., Del Bondio, A., Baderna, V., et al. (2019). Pathogenic variants in the AFG3L2 proteolytic domain cause SCA28 through haploinsufficiency and proteostatic stress-driven OMA1 activation. *Journal of Medical Genetics*, 56(8), 499–511. <https://doi.org/10.1136/jmedgenet-2018-105766>
- Uchinomiya, S., Matsunaga, N., Kamoda, K., et al. (2020). Fluorescence detection of metabolic activity of the fatty acid beta oxidation pathway in living cells. *Chemical Communications*, 56(20), 3023–3026. <https://doi.org/10.1039/c9cc09993j>
- Udeani, G., Zhao, G., Shin, Y., et al. (2001). Pharmacokinetics of deguelin, a cancer chemopreventive agent in rats. *Cancer Chemotherapy and Pharmacology*, 47(3), 263–268. <https://doi.org/10.1007/S002800000187>
- Um, J. H., Kim, Y. Y., Finkel, T., et al. (2018). Sensitive measurement of mitophagy by flow cytometry using the pH-dependent fluorescent reporter mt-Keima. *Journal of Visualized Experiments*, 2018(138). <https://doi.org/10.3791/58099>
- US-EPA, United States Environmental Protection Agency (2020). New approach methods work plan: Reducing use of animals in chemical testing. U.S. Environmental Protection Agency, Washington, DC. EPA 615B2001 [https://www.epa.gov/sites/production/files/2020-06/documents/epa\\_nam\\_work\\_plan.pdf](https://www.epa.gov/sites/production/files/2020-06/documents/epa_nam_work_plan.pdf)
- Valente, E. M., Abou-Sleiman, P. M., Caputo, V., et al. (2004). Hereditary early-onset Parkinson's disease caused by mutations in PINK1. *Science*, 304(5674), 1158–1160. <https://doi.org/10.1126/science.1096284>

- Van Den Bogert, C., Spelbrink, J. N., & Dekker, H. L. (1992). Relationship between culture conditions and the dependency on mitochondrial function of mammalian cell proliferation. *Journal of Cellular Physiology*, 152(3), 632–638. <https://doi.org/10.1002/jcp.1041520323>
- van der Stel, W., Carta, G., Eakins, J., Darici, S., Delp, J., A, F., et al. (2020). Multiparametric assessment of mitochondrial respiratory inhibition in HepG2 and RPTEC/TERT1 cells using a panel of mitochondrial targeting agrochemicals. *Archives of Toxicology*, 94(8), 2707–2729. <https://doi.org/10.1007/S00204-020-02792-5>
- van Ravenzwaay, B., Cunha, G. C. P., Leibold, E., et al. (2007). The use of metabolomics for the discovery of new biomarkers of effect. *Toxicology Letters*, 172(1–2), 21–28. <https://doi.org/10.1016/j.toxlet.2007.05.021>
- Van Ravenzwaay, B., Herold, M., Kamp, H., et al. (2012). Metabolomics: A tool for early detection of toxicological effects and an opportunity for biology based grouping of chemicals-From QSAR to QBAR. *Mutation Research - Genetic Toxicology and Environmental Mutagenesis*, 746(2), 144–150. <https://doi.org/10.1016/j.mrgentox.2012.01.006>
- van Ravenzwaay, B., Sperber, S., Lemke, O., et al. (2016). Metabolomics as read-across tool: A case study with phenoxy herbicides. *Regulatory Toxicology and Pharmacology*, 81, 288–304. <https://doi.org/10.1016/j.yrtph.2016.09.013>
- van Riel, N. A. W. (2006). Dynamic modelling and analysis of biochemical networks: Mechanism-based models and model-based experiments. In *Briefings in Bioinformatics* (Vol. 7, Issue 4, pp. 364–374). Brief Bioinform. <https://doi.org/10.1093/bib/bbl040>
- Van Summeren, A., Renes, J., Van Delft, J. H. M., et al. (2012). Proteomics in the search for mechanisms and biomarkers of drug-induced hepatotoxicity. In *Toxicology in Vitro* (Vol. 26, Issue 3, pp. 373–385). <https://doi.org/10.1016/j.tiv.2012.01.012>
- Vander Heiden, M. G., Cantley, L. C., & Thompson, C. B. (2009). Understanding the warburg effect: The metabolic requirements of cell proliferation. In *Science* (Vol. 324, Issue 5930, pp. 1029–1033). <https://doi.org/10.1126/science.1160809>
- Vasan, K., Werner, M., & Chandel, N. S. (2020). Mitochondrial Metabolism as a Target for Cancer Therapy. In *Cell Metabolism* (Vol. 32, Issue 3, pp. 341–352). Cell Press. <https://doi.org/10.1016/j.cmet.2020.06.019>
- Villeneuve, D., D, C., N, G.-R., et al. (2014). Adverse outcome pathway (AOP) development I: strategies and principles. *Toxicological Sciences: An Official Journal of the Society of Toxicology*, 142(2), 312–320. <https://doi.org/10.1093/TOXSCI/KFU199>
- Villeneuve, D. L., Crump, D., Garcia-Reyero, N., et al. (2014a). Adverse outcome pathway (AOP) development I: Strategies and principles. *Toxicological Sciences*, 142(2), 312–320. <https://doi.org/10.1093/toxsci/kfu199>
- Villeneuve, D. L., Crump, D., Garcia-Reyero, N., et al. (2014b). Adverse outcome pathway development II: Best practices. *Toxicological Sciences*, 142(2), 321–330. <https://doi.org/10.1093/toxsci/kfu200>
- Vinken, M. (2013). The adverse outcome pathway concept: A pragmatic tool in toxicology. In *Toxicology* (Vol. 312, pp. 158–165). <https://doi.org/10.1016/j.tox.2013.08.011>
- von Jagow, G., & TA, L. (1986). Use of specific inhibitors on the mitochondrial bc1 complex. *Methods in Enzymology*, 126(C), 253–271. [https://doi.org/10.1016/S0076-6879\(86\)26026-7](https://doi.org/10.1016/S0076-6879(86)26026-7)
- von Stechow, L., Ruiz-Aracama, A., van de Water, B., et al. (2013). Identification of Cisplatin-Regulated Metabolic Pathways in Pluripotent Stem Cells. *PLoS ONE*, 8(10), e76476. <https://doi.org/10.1371/journal.pone.0076476>
- Voos, W., & Röttgers, K. (2002). Molecular chaperones as essential mediators of mitochondrial biogenesis. In *Biochim Biophys Acta* (Vol. 1592, Issue 1, pp. 51–62). [https://doi.org/10.1016/S0167-4889\(02\)00264-1](https://doi.org/10.1016/S0167-4889(02)00264-1)
- Vowinckel, J., Hartl, J., Butler, R., et al. (2015). MitoLoc: A method for the simultaneous quantification of mitochondrial network morphology and membrane potential in single cells. *Mitochondrion*, 24, 77–86. <https://doi.org/10.1016/j.mito.2015.07.001>
- Vuckovic, D. (2012). Current trends and challenges in sample preparation for global metabolomics using liquid chromatography-mass spectrometry. In *Analytical and Bioanalytical Chemistry* (Vol. 403, Issue 6, pp. 1523–1548). <https://doi.org/10.1007/s00216-012-6039-y>
- Waldeck-Weiermair, M., Gottschalk, B., Madreiter-Sokolowski, C. T., et al. (2019). Development and Application of Sub-Mitochondrial Targeted Ca<sup>2+</sup> Biosensors. *Frontiers in Cellular Neuroscience*, 13, 449. <https://doi.org/10.3389/fncel.2019.00449>
- Waldmann, T., Rempel, E., Balmer, N. V., König, A., et al. (2014). Design principles of concentration-dependent transcriptome deviations in drug-exposed differentiating stem cells. *Chemical Research in Toxicology*, 27(3), 408–420. <https://doi.org/10.1021/tx400402j>
- Waldmeier, P. C., Feldtrauer, J. J., Qian, T., et al. (2002). Inhibition of the mitochondrial permeability transition by the nonimmunosuppressive cyclosporin derivative NIM811. *Molecular Pharmacology*, 62(1), 22–29. <https://doi.org/10.1124/mol.62.1.22>
- Wallace, D. C., & Chalkia, D. (2013). Mitochondrial DNA genetics and the heteroplasmy conundrum in evolution and disease. *Cold Spring Harbor Perspectives in Biology*, 5(11), a021220. <https://doi.org/10.1101/cshperspect.a021220>
- Wan, B., LaNoue, K. F., Cheung, J. Y., et al. (1989). Regulation of citric acid cycle by calcium. *Journal of Biological Chemistry*, 264(23), 13430–13439.
- Wang, A., Costello, S., Cockburn, M., et al. (2011). Parkinson's disease risk from ambient exposure to pesticides. *European Journal of Epidemiology*, 26(7), 547–555. <https://doi.org/10.1007/s10654-011-9574-5>
- Wang, L., Yuan, L., Zeng, X., et al. (2016). A Multisite-Binding Switchable Fluorescent Probe for Monitoring Mitochondrial ATP Level Fluctuation in Live Cells. *Angewandte Chemie - International Edition*, 55(5), 1773–1776. <https://doi.org/10.1002/anie.201510003>
- Wang, X. D., & Wolfbeis, O. S. (2014). Optical methods for sensing and imaging oxygen: Materials, spectroscopies and applications. In *Chemical Society Reviews* (Vol. 43, Issue 10, pp. 3666–3761). Royal Society of Chemistry. <https://doi.org/10.1039/c4cs00039k>

- Wang, Z. M., Ying, Z., Bosy-Westphal, A., et al. (2010). Specific metabolic rates of major organs and tissues across adulthood: Evaluation by mechanistic model of resting energy expenditure. *American Journal of Clinical Nutrition*, 92(6), 1369–1377. <https://doi.org/10.3945/ajcn.2010.29885>
- Ward, J. H. (1963). Hierarchical Grouping to Optimize an Objective Function. *Journal of the American Statistical Association*, 236–244. <https://doi.org/10.1080/01621459.1963.10500845>
- West, A. P., Khoury-Hanold, W., Staron, M., et al. (2015). Mitochondrial DNA stress primes the antiviral innate immune response. *Nature*, 520(7548), 553–557. <https://doi.org/10.1038/nature14156>
- Westermann, B. (2010). Mitochondrial fusion and fission in cell life and death. In *Nature Reviews Molecular Cell Biology* (Vol. 11, Issue 12, pp. 872–884). <https://doi.org/10.1038/nrm3013>
- Westrate, L. M., Drocco, J. A., Martin, K. R., et al. (2014). Mitochondrial morphological features are associated with fission and fusion events. *PLoS ONE*, 9(4), e95265. <https://doi.org/10.1371/journal.pone.0095265>
- Wetmore, B. A., & Merrick, B. A. (2004). Toxicoproteomics: Proteomics applied to toxicology and pathology. In *Toxicologic Pathology* (Vol. 32, Issue 6, pp. 619–642). <https://doi.org/10.1080/01926230490518244>
- Wickham, H., (2007). Reshaping Data with the reshape Package. *Journal of Statistical Software*, 21(12), 1-20. URL <http://www.jstatsoft.org/v21/i12/>.
- Wickham, H., (2011). The Split-Apply-Combine Strategy for Data Analysis. *Journal of Statistical Software*, 40(1), 1-29. URL <http://www.jstatsoft.org/v40/i01/>.
- Wickham, H., (2016). ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag New York, <https://CRAN.R-project.org/package=ggplot2>
- Wickham, H., Bryan, J., (2019). readxl: Read Excel Files. R package version 1.3.1. <https://CRAN.R-project.org/package=readxl>
- Wickham, H., (2019). stringr: Simple, Consistent Wrappers for Common String Operations. R package version 1.4.0. <https://CRAN.R-project.org/package=stringr>
- Wickham, H., Seidel, D., (2020). scales: Scale Functions for Visualization. R package version 1.1.1. <https://CRAN.R-project.org/package=scales>
- Wickham, H., (2020). tidyr: Tidy Messy Data. R package version 1.1.2. <https://CRAN.R-project.org/package=tidyr>
- Will, Y., & Dykens, J. (2014). Mitochondrial toxicity assessment in industry—a decade of technology development and insight. *Expert Opinion on Drug Metabolism and Toxicology*, 10(8), 1061–1067. <https://doi.org/10.1517/17425255.2014.939628>
- Wickham, H., François, R., Henry, L., Müller, K., (2021). dplyr: A Grammar of Data Manipulation. R package version 1.0.4. <https://CRAN.R-project.org/package=dplyr>
- Wiederschain, G. Y. (2011). The Molecular Probes handbook. A guide to fluorescent probes and labeling technologies. *Biochemistry (Moscow)*, 76(11), 1276–1276. <https://doi.org/10.1134/s0006297911110101>
- Will, Y., & Dykens, J. (2014). Mitochondrial toxicity assessment in industry—a decade of technology development and insight. In *Expert Opinion on Drug Metabolism and Toxicology* (Vol. 10, Issue 8, pp. 1061–1067). <https://doi.org/10.1517/17425255.2014.939628>
- Will, Y., Hynes, J., Ogurtsov, V. I., et al. (2007). Analysis of mitochondrial function using phosphorescent oxygen-sensitive probes. *Nature Protocols*, 1(6), 2563–2572. <https://doi.org/10.1038/nprot.2006.351>
- Will, Y., Shields, J. E., & Wallace, K. B. (2019). Drug-induced mitochondrial toxicity in the geriatric population: Challenges and future directions. In *Biology* (Vol. 8, Issue 2, p. 32). <https://doi.org/10.3390/biology8020032>
- Williams, B. B., Khan, N., Zaki, B., et al. (2010). Clinical electron paramagnetic resonance (EPR) oximetry using India ink. *Advances in Experimental Medicine and Biology*, 662, 149–156. [https://doi.org/10.1007/978-1-4419-1241-1\\_21](https://doi.org/10.1007/978-1-4419-1241-1_21)
- Williams, E. G., Wu, Y., Jha, P., et al. (2016). Systems proteomics of liver mitochondria function. *Science*, 352(6291), aad0189. <https://doi.org/10.1126/science.aad0189>
- Wills, L. P., Beeson, G. C., Hoover, D. B., et al. (2015). Assessment of ToxCast phase II for mitochondrial liabilities using a high-throughput respirometric assay. *Toxicological Sciences*, 146(2), 226–234. <https://doi.org/10.1093/toxsci/kfv085>
- Wilmes, A., Bielow, C., Ranninger, C., et al. (2015). Mechanism of cisplatin proximal tubule toxicity revealed by integrating transcriptomics, proteomics, metabolomics and biokinetics. *Toxicology in Vitro*, 30(1 Pt A), 117–127. <https://doi.org/10.1016/j.tiv.2014.10.006>
- Wilmes, A., Limonciel, A., Aschauer, L., et al. (2013). Application of integrated transcriptomic, proteomic and metabolomic profiling for the delineation of mechanisms of drug induced cell stress. *Journal of Proteomics*, 79, 180–194. <https://doi.org/10.1016/j.jprot.2012.11.022>
- Wilson, T., & Woodland Hastings, J. (1998). Bioluminescence. In *Annual Review of Cell and Developmental Biology* (Vol. 14, pp. 197–230). *Annu Rev Cell Dev Biol*. <https://doi.org/10.1146/annurev.cellbio.14.1.197>
- Wink, S., Hiemstra, S., Hoppers, B., et al. (2017). High-content imaging-based BAC-GFP toxicity pathway reporters to assess chemical adversity liabilities. *Archives of Toxicology*, 91(3), 1367–1383. <https://doi.org/10.1007/s00204-016-1781-0>
- Wink, S., Hiemstra, S., Huppelschoten, S., et al. (2014). Quantitative high content imaging of cellular adaptive stress response pathways in toxicity for chemical safety assessment. In *Chemical Research in Toxicology* (Vol. 27, Issue 3, pp. 338–355). <https://doi.org/10.1021/tx4004038>
- Wink, S., Hiemstra, S. W., Huppelschoten, S., et al. (2018). Dynamic imaging of adaptive stress response pathway activation for prediction of drug induced liver injury. *Archives of Toxicology*, 92(5), 1797–1814. <https://doi.org/10.1007/s00204-018-2178-z>
- Witten, D., (2019). PoiCluClu: Classification and Clustering of Sequencing Data Based on a Poisson Model. R package version 1.0.2.1. <https://CRAN.R-project.org/package=PoiCluClu>



- Wittenberg, J. B. (1970). Myoglobin-facilitated oxygen diffusion: role of myoglobin in oxygen entry into muscle. In *Physiological reviews* (Vol. 50, Issue 4, pp. 559–636). <https://doi.org/10.1152/physrev.1970.50.4.559>
- Wojtczak, L., & Zablocki, K. (2008). Basic Mitochondrial Physiology in Cell Viability and Death. In *Drug-Induced Mitochondrial Dysfunction* (pp. 1–35). John Wiley & Sons, Inc. <https://doi.org/10.1002/9780470372531.ch1>
- Wolters, J. E. J., Van Herwijnen, M. H. M., Theunissen, D. H. J., et al. (2016). Integrative “-Omics” Analysis in Primary Human Hepatocytes Unravels Persistent Mechanisms of Cyclosporine A-Induced Cholestasis. *Chemical Research in Toxicology*, 29(12), 2164–2174. <https://doi.org/10.1021/acs.chemrestox.6b00337>
- Wood, E., Latli, B., & Casida, J. E. (1996). Fenazaquin Acaricide Specific Binding Sites in NADH: Ubiquinone Oxidoreductase and Apparently the ATP Synthase Stalk. *Pesticide Biochemistry and Physiology*, 54(2), 135–145. <https://doi.org/10.1006/PEST.1996.0017>
- World Health Organization (2010) International Programme on Chemical Safety & Inter-Organization Programme for the Sound Management of Chemicals. Characterization and application of physiologically based pharmacokinetic models in risk assessment. <https://apps.who.int/iris/handle/10665/44495>
- Wu, C. C., Luk, H. N., Lin, Y. T. T., et al. (2010). A Clark-type oxygen chip for in situ estimation of the respiratory activity of adhering cells. *Talanta*, 81(1–2), 228–234. <https://doi.org/10.1016/j.talanta.2009.11.062>
- Wu, F., Yang, F., Vinnakota, K. C., et al. (2007). Computer modeling of mitochondrial tricarboxylic acid cycle, oxidative phosphorylation, metabolite transport, and electrophysiology. *Journal of Biological Chemistry*, 282(34), 24525–24537. <https://doi.org/10.1074/jbc.M701024200>
- Xia, M., Huang, R., Shi, Q., et al. (2018a). Comprehensive analyses and prioritization of Tox21 10K chemicals affecting mitochondrial function by in-depth mechanistic studies. *Environmental Health Perspectives*, 126(7), 077010. <https://doi.org/10.1289/EHP2589>
- Xu, Z., Singh, N. J., Lim, J., et al. (2009). Unique sandwich stacking of pyrene-adenine-pyrene for selective and ratiometric fluorescent sensing of ATP at physiological pH. *Journal of the American Chemical Society*, 131(42), 15528–15533. <https://doi.org/10.1021/ja906855a>
- Yaginuma, H., Kawai, S., Tabata, K. V., et al. (2014). Diversity in ATP concentrations in a single bacterial cell population revealed by quantitative single-cell imaging. *Scientific Reports*, 4, 6522. <https://doi.org/10.1038/srep06522>
- Yang, H., Meijer, H. G. E., Buitenveg, J. R., et al. (2016). Estimation and identifiability of model parameters in human nociceptive processing using yes-no detection responses to electrocutaneous stimulation. *Frontiers in Psychology*, 7, 1884. <https://doi.org/10.3389/fpsyg.2016.01884>
- Yang, H., Niemeijer, M., van de Water, B., et al. (2020). ATF6 Is a Critical Determinant of CHOP Dynamics during the Unfolded Protein Response. *iScience*, 23(2), 100860. <https://doi.org/10.1016/j.isci.2020.100860>
- Yang, Y., Nadanaciva, S., Will, Y., et al. (2015). MITOSym@: A mechanistic, mathematical model of hepatocellular respiration and bioenergetics. *Pharmaceutical Research*, 32(6), 1975–1992. <https://doi.org/10.1007/s11095-014-1591-0>
- Ye, J., Kumanova, M., Hart, L. S., et al. (2010). The GCN2-ATF4 pathway is critical for tumour cell survival and proliferation in response to nutrient deprivation. *EMBO Journal*, 29(12), 2082–2096. <https://doi.org/10.1038/emboj.2010.81>
- Yeakley, J., Shepard, P., Goyena, D., et al. (2017). A trichostatin A expression signature identified by TempO-Seq targeted whole transcriptome profiling. *PLoS One*, 12(5). <https://doi.org/10.1371/JOURNAL.PONE.0178302>
- Yen, K., Lee, C., Mehta, H., et al. (2012). The emerging role of the mitochondrial-derived peptide humanin in stress resistance. In *Journal of Molecular Endocrinology* (Vol. 50, Issue 1, pp. R11–R19). <https://doi.org/10.1530/JME-12-0203>
- Yépez, V. A., Kremer, L. S., Iuso, A., et al. (2018). OCR-Stats: Robust estimation and statistical testing of mitochondrial respiration activities using Seahorse XF analyzer. *PLoS ONE*, 13(7), e0199938. <https://doi.org/10.1371/journal.pone.0199938>
- Yi, H. S., Chang, J. Y., & Shong, M. (2018). The mitochondrial unfolded protein response and mitohormesis: A perspective on metabolic diseases. In *Journal of Molecular Endocrinology* (Vol. 61, Issue 3, pp. R91–R105). <https://doi.org/10.1530/JME-18-0005>
- Youle, R. J., & Narendra, D. P. (2011). Mechanisms of mitophagy. *Nature Reviews Molecular Cell Biology*, 12(1), 9–14. <https://doi.org/10.1038/nrm3028>
- Youle, R. J., & Van Der Bliek, A. M. (2012). Mitochondrial fission, fusion, and stress. In *Science* (Vol. 337, Issue 6098, pp. 1062–1065). <https://doi.org/10.1126/science.1219855>
- Yuan, L., & Kaplowitz, N. (2013). Mechanisms of drug-induced liver injury. In *Clinics in Liver Disease* (Vol. 17, Issue 4, pp. 507–518). W.B. Saunders. <https://doi.org/10.1016/j.cld.2013.07.002>
- Yumnamcha, T., Devi, T. S., & Singh, L. P. (2019). Auranofin Mediates Mitochondrial Dysregulation and Inflammatory Cell Death in Human Retinal Pigment Epithelial Cells: Implications of Retinal Neurodegenerative Diseases. *Frontiers in Neurosciences*, 13, 1065. <https://doi.org/10.3389/fnins.2019.01065>
- Zachar, Z., Marecek, J., Maturo, C., et al. (2011). Non-redox-active lipoate derivatives disrupt cancer cell mitochondrial metabolism and are potent anticancer agents in vivo. *Journal of Molecular Medicine*, 89(11), 1137–1148. <https://doi.org/10.1007/s00109-011-0785-8>
- Zahedi, A., On, V., Phandthong, R., et al. (2018). Deep Analysis of Mitochondria and Cell Health Using Machine Learning. *Scientific Reports*, 8(1), 1–15. <https://doi.org/10.1038/s41598-018-34455-y>
- Zeileis, A., Fisher, J. C., Hornik, K., et al. (2020). Colorspace: A toolbox for manipulating and assessing colors and palettes. *Journal of Statistical Software*. <https://doi.org/10.18637/jss.v096.i01>

- Zgheib, E., Gao, W., Limonciel, A., et al. (2019). Application of three approaches for quantitative AOP development to renal toxicity. *Computational Toxicology*, 11, 1–13. <https://doi.org/10.1016/j.comtox.2019.02.001>
- Zhang, H., Chen, Q. Y., Xiang, M. L., et al. (2009). In silico prediction of mitochondrial toxicity by using GA-CG-SVM approach. *Toxicology in Vitro*, 23(1), 134–140. <https://doi.org/10.1016/j.tiv.2008.09.017>
- Zhao, P., Wang, L., Zhu, X., et al. (2010). Subnanomolar inhibitor of cytochrome bc<sub>1</sub> complex designed by optimizing interaction with conformationally flexible residues. *Journal of the American Chemical Society*, 132(1), 185–194. <https://doi.org/10.1021/JA905756C>
- Zhao, X. Y., Lu, M. H., Yuan, D. J., et al. (2019). Mitochondrial dysfunction in neural injury. In *Frontiers in Neuroscience* (Vol. 13, p. 30). <https://doi.org/10.3389/fnins.2019.00030>
- Zhao, Y., Araki, S., Wu, J., et al. (2011). An expanded palette of genetically encoded Ca<sup>2+</sup> indicators. *Science*, 333(6051), 1888–1891. <https://doi.org/10.1126/science.1208592>
- Zhao, Y., & Jensen, O. N. (2009). Modification-specific proteomics: Strategies for characterization of post-translational modifications using enrichment techniques. In *Proteomics* (Vol. 9, Issue 20, pp. 4632–4641). <https://doi.org/10.1002/pmic.200900398>
- Zhong, X., da Silveira e Sá, R. de C., & Zhong, C. (2017). Mitochondrial biogenesis in response to chromium (VI) toxicity in human liver cells. *International Journal of Molecular Sciences*, 18(9), 1877. <https://doi.org/10.3390/ijms18091877>
- Zhong, Y., Li, X., Yu, D., et al. (2015). Application of mitochondrial pyruvate carrier blocker UK5099 creates metabolic reprogram and greater stem-like properties in LnCap prostate cancer cells in vitro. *Oncotarget*, 6(35), 37758–37769. <https://doi.org/10.18632/oncotarget.5386>
- Zhou, Y., Zhang, S., He, H., et al. (2018). Design and synthesis of highly selective pyruvate dehydrogenase complex E1 inhibitors as bactericides. *Bioorganic and Medicinal Chemistry*, 26(1), 84–95. <https://doi.org/10.1016/j.bmc.2017.11.021>
- Zhou, Z., Austin, G., Young, L., et al. (2018). Mitochondrial Metabolism in Major Neurological Diseases. *Cells*, 7(12), 229. <https://doi.org/10.3390/cells7120229>
- Zoetewij, J. P., Van De Water, B., De Bont, H. J. G. M., et al. (1994). Mitochondrial K<sup>+</sup> as modulator of Ca<sup>2+</sup>-dependent cytotoxicity in hepatocytes. Novel application of the K<sup>+</sup>-sensitive dye PBFI (K<sup>+</sup>-binding benzofuran isophthalate) to assess free mitochondrial K<sup>+</sup> concentrations. *Biochemical Journal*, 299(Pt 2), 539–543. <https://doi.org/10.1042/bj2990539>
- Züchner, S., Mersiyanova, I. V., Muglia, M., et al. (2004). Mutations in the mitochondrial GTPase mitofusin 2 cause Charcot-Marie-Tooth neuropathy type 2A. *Nature Genetics*, 36(5), 449–451. <https://doi.org/10.1038/ng1341>
- Zukunft, S., Prehn, C., Röhring, C., et al. (2018). High-throughput extraction and quantification method for targeted metabolomics in murine tissues. *Metabolomics*, 14(1), 18. <https://doi.org/10.1007/s11306-017-1312-x>

## Websites

1. <https://www.khanacademy.org/science/biology/membranes-and-transport/active-transport/a/active-transport>, accessed April 2021
2. <https://www.khanacademy.org/science/biology/cell-signaling/mechanisms-of-cell-signaling/a/intracellular-signal-transduction>, accessed April 2021
3. <https://aopwiki.org/aops>; accessed April 2021
4. <https://www.oecd.org/chemicalsafety/testing/adverse-outcome-pathways-molecular-screening-and-toxicogenomics.htm>; accessed April 2021
5. <https://www.uniprot.org/uniprot/Q9Y5U8>; accessed April 2021
6. [https://www.malacards.org/card/mitochondrial\\_pyruvate\\_carrier\\_deficiency](https://www.malacards.org/card/mitochondrial_pyruvate_carrier_deficiency); accessed April 2021
7. <https://www.genecards.org/cgi-bin/carddisp.pl?gene=MPC2&keywords=MPC2>; accessed April 2021
8. <https://ghr.nlm.nih.gov/condition/pyruvate-dehydrogenase-deficiency>; accessed April 2021
9. <https://clinicaltrials.gov/ct2/home>; accessed April 2021
10. [https://www.ncbi.nlm.nih.gov/nuccore/NC\\_012920.1](https://www.ncbi.nlm.nih.gov/nuccore/NC_012920.1); accessed April 2021
11. <https://www.frac.info/>; (FRAC poster 2021 (R) accessed April 2021
12. <https://medlineplus.gov/genetics/condition/charcot-marie-tooth-disease/#inheritance>; accessed April 2021
13. [http://amp.pharm.mssm.edu/Harmonizome/gene\\_set/Glycolysis/PANTHER+Pathways](http://amp.pharm.mssm.edu/Harmonizome/gene_set/Glycolysis/PANTHER+Pathways); accessed October 2021
14. [http://brainarray.mbni.med.umich.edu/Brainarray/Database/CustomCDF/genomic\\_curated\\_CDF.asp](http://brainarray.mbni.med.umich.edu/Brainarray/Database/CustomCDF/genomic_curated_CDF.asp); HGU133Plus2 array version, accessed June 2021.
15. <https://github.com/mcs07/PubChemPy>; accessed October 2021
16. <https://amp.pharm.mssm.edu/archs4/gene/KLHL24>; accessed October 2021
17. <https://www.genecards.org/>; accessed October 2021
18. <https://www.fda.gov/science-research/liver-toxicity-knowledge-base-ltkb/drug-induced-liver-injury-rank-dilirank-dataset>; accessed October 2021
19. <https://bioconductor.org/packages/release/bioc/html/rhdf5.html>; accessed 1 June 2021
20. <https://www.eu-toxrisk.eu/>, accessed March 2021
21. <http://www.oecd.org/chemicalsafety/risk-assessment/iata-integrated-approaches-to-testing-and-assessment.htm>; accessed March 2021
22. <https://aopwiki.org/aops/3>; accessed June 2021
23. <http://www.rdkit.org/>; accessed March 2021
24. <http://comptox.epa.gov/dashboard>; accessed March 2021
25. <http://chem.nlm.nih.gov/chemidplus/>; accessed March 2021
26. <https://smartsview.zbh.uni-hamburg.de/>; accessed March 2021

## Abbreviations

2D	two-dimensional	KD	knock down
3D	three-dimensional	KP	kinase pool
2DG	2-deoxy glucose	MEP	mepronil
AA	antimycin a	mito	mitochondria
ADP	adenosine diphosphate	MMP	mitochondrial membrane potential
AIC	akaike information criterion	mt	mitochondrial
AOP	adverse outcome pathway	N.C.	negative control
APS	ammonium persulfate	NES	normalized enrichment score
ATP	adenosine triphosphate	nuc	nuclear
AZO	azoxystrobin	O/N	overnight
BAC	bacterial artificial chromosome	OCR	oxygen consumption rate
BMC	bench mark concentration	N.C.	negative control
CAP	capsaicin	NES	normalized enrichment score
CAR	carboxin	O/N	overnight
CDDO-me	bardoxolone methyl	OCR	oxygen consumption rate
cDNA	complementary DNA	OLI	oligomycin
CFP	cyan fluorescent protein	OSR	oxidative stress response
cMax	maximal concentration in plasm	OXPPOS	oxidative phosphorylation
CSA	cyclosporine a	P.C.	positive control
CYA	cyazofamid	padj	adjusted p-value
cyt	cytoplasmic	PBS	phosphate-buffered saline
DCCD/DCC	N,N'-Dicyclohexylcarbodiimide	PCR	polymerase chain reaction
DDR	DNA damage response	PenStrep	penicillin-streptomycin
DEG	differential expressed genes (transcriptomics context)	PHH	primary human hepatocytes
DEG	deguelin (compoun context)	PI	propidium iodide
DEM	diethyl maleate	PIC	pixocystrobin
DIA	diafenthuron	PMD	pyrimidifen
DILI	drug-induced liver injury	pme	Plasma-membrane-targeted
DMEM	dulbecco's modified eagle's medium	PVDF	polyvinylidene difluoride
DMSO	dimethyl sulfoxide	PYR	pyraclostrobin
DNA	deoxyribonucleic acid	Rho123	rhodamine123
EC50	half maximal effective concentration	RNA	ribonucleic acid
EGS	eigengene Score	ROS	reactive oxygen species
ER	Endoplasmic reticulum	ROT	rotenone
ETC	electron transport chain	RT	room temperature
FAO	Fatty acid oxidation	SD	standard deviation
FBS	fetal bovine serum	siRNA	small interfering RNA
FC	fold change	TEB	tebufenpyrad
FCCP	Carbonyl cyanide 4-(trifluoromethoxy) phenylhydrazone	TF	transcription factor
FP	Fluorophore/ fluorescent protein	TGGATES	Toxicogenomics Project-Genomics Assisted Toxicity Evaluation System
FPX	fenpyroximate	THI	thifluzamide
FRET	fluorescence resonance energy transfer	TNFa	tumour necrosis factor alpha
Gal	galactose	TP	time point
GFP	green fluorescent protein	untr	untreated
Glu	glucose	UPR	unfolded protein response
GO	gene ontology	VAL	valinomycin
IC50	half maximal inhibitory concentration	WB	Western blot
IF	Immuno fluorescence	WGCNA	weighted gene correlation network analysis
		YFP	yellow fluorescent protein